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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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Medical

SURGERY

VOL. 35 JANUARY, 1954 NO. 1

Original Communications

Society for Vascular Surgery
(concluded)

AN EVALUATION OF "HIGH" LUMBAR SYMPATHECTOMY IN ARTERIOSCLEROTIC CIRCULATORY INSUFFICIENCY OF THE LOWER EXTREMITIES

GEORGE D. LILLY, M.D., DONALD W. SMITH, M.D.,
CHARLES F. BIGGANE, JR., M.D., AND JOSEPH T. JANA, JR., M.D.,
MIAMI, FLA.

SEVERAL years ago we[1] made the observation that individuals upon whom thoracolumbar sympathectomies had been performed for hypertension seemed to have more complete sympathectomies of the lower extremities than did individuals on whom the classical lumbar sympathectomies had been performed for peripheral vascular disease of the lower extremities. This caused us to change our technique for performing lumbar sympathectomies, and since 1948 we have, routinely, performed lower extremity sympathectomies by resecting the distal two-thirds of the twelfth rib and, through the bed of this rib, extending an incision forward and downward toward the umbilicus to expose the sympathetic trunk (Fig. 1), retroperitoneally, where it emerges from the diaphragm. Through such an incision, we are able to remove the upper three lumbar ganglia and, by splitting the crus of the diaphragm (Fig. 2), the twelfth thoracic ganglion can be removed. The removal of these four ganglia can be accomplished quickly without undue retraction and with clear visualization of the entire area through such an incision.

We are of the opinion that such a procedure accomplishes a complete sympathetic denervation of the entire lower extremity. We feel that the better exposure affords a much greater degree of protection against hemorrhage and that the avoidance of excessive retraction, which is necessary in the usual type of lumbar sympathectomy, reduces the incidence of postsympathectomy causalgia and genitofemoral neuralgia.

In recent weeks we have learned that Coldwater, Cox, Randall, Alexander, and Hertzman[2] have been employing a similar approach. They have found

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that by stimulating the various ganglia at the time of surgery they were able to demonstrate that sympathetic innervation to all parts of the lower extremity is frequently derived from as high as the first lumbar ganglion, and as low as the fifth lumbar ganglion. Their clinical results, both in primary operation and in secondary operation where previous "low" sympathectomy had proved to be unsatisfactory, have been most gratifying, and their enthusiam for total lumbar sympathectomy seems to compare with our own. They[4] have shown by animal investigation that such variations in sympathetic pathways do exist.

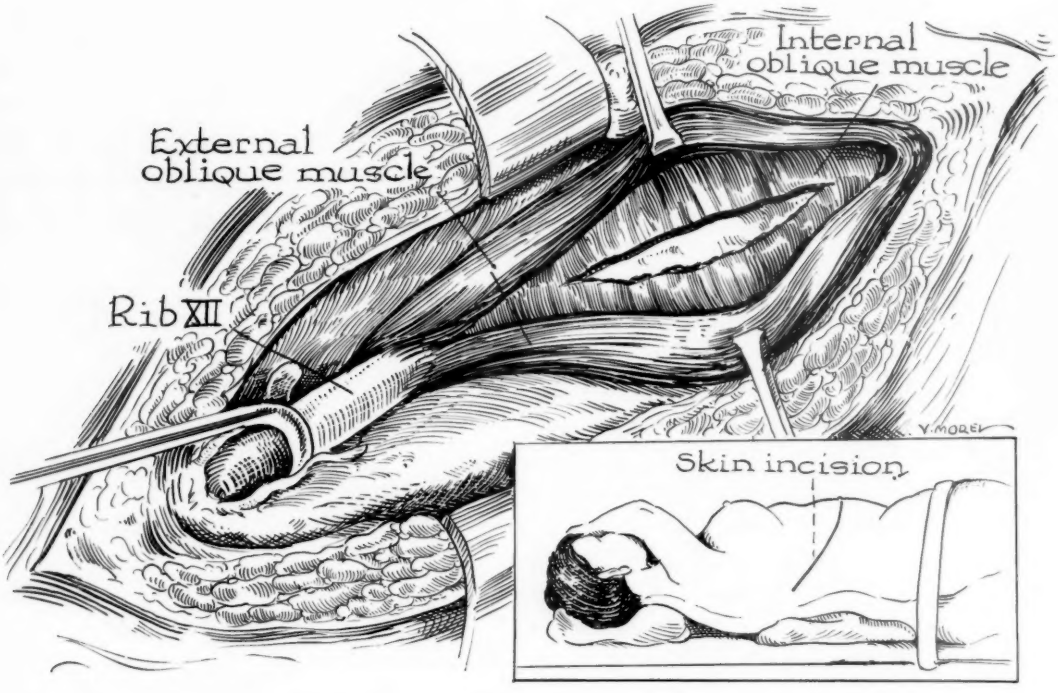

Fig. 1.—The patient is placed on a sandbag with the operative side up at an angle of forty-five degrees. Immobilization is assured by a wide adhesive strip across the hips.

The incision is made in the line of the twelfth rib and carried forward toward the umbilicus to the lateral edge of the rectus muscle.

The distal two-thirds of the twelfth rib is resected subperiosteally, and the oblique muscles are divided in the same line. Care is exercised to avoid injury to the intercostal nerves. The retroperitoneal space is entered. The peritoneum and, on the right side, the vena cava are retracted anteriorly.

Francioli,[5] also, has recently advocated approaching the lumbar sympathetic ganglia from a "high" incision through the bed of the twelfth rib.

Since Royle[3] first described his approach to the lumbar ganglia, various modifications have been described.[6, 7] Longitudinal, transverse, oblique, and curved skin incisions have been employed, and various techniques of muscle splitting and muscle cutting have been advocated. All of these entail an approach to the sympathetic trunk at the level of the fourth lumbar vertebral body; then, by retraction upon the renal pedicle and, on the right side, the vena cava, some of the upper ganglia are removed. In the obese "short-coupled" individual it is difficult to expose any part of the sympathetic trunk through

such an incision and, under the most ideal circumstances, it is frequently impossible to remove the second lumbar ganglion by this approach. When the upper lumbar ganglia are exposed, or removed blindly,[6] through such an incision, there is great danger of tearing a large lumbar vein where it enters the vena cava, particularly since the first and second lumbar veins frequently pass anterior to the sympathetic trunk on the right side. Injury to the vena cava, or even the renal vessels, is another definite danger.

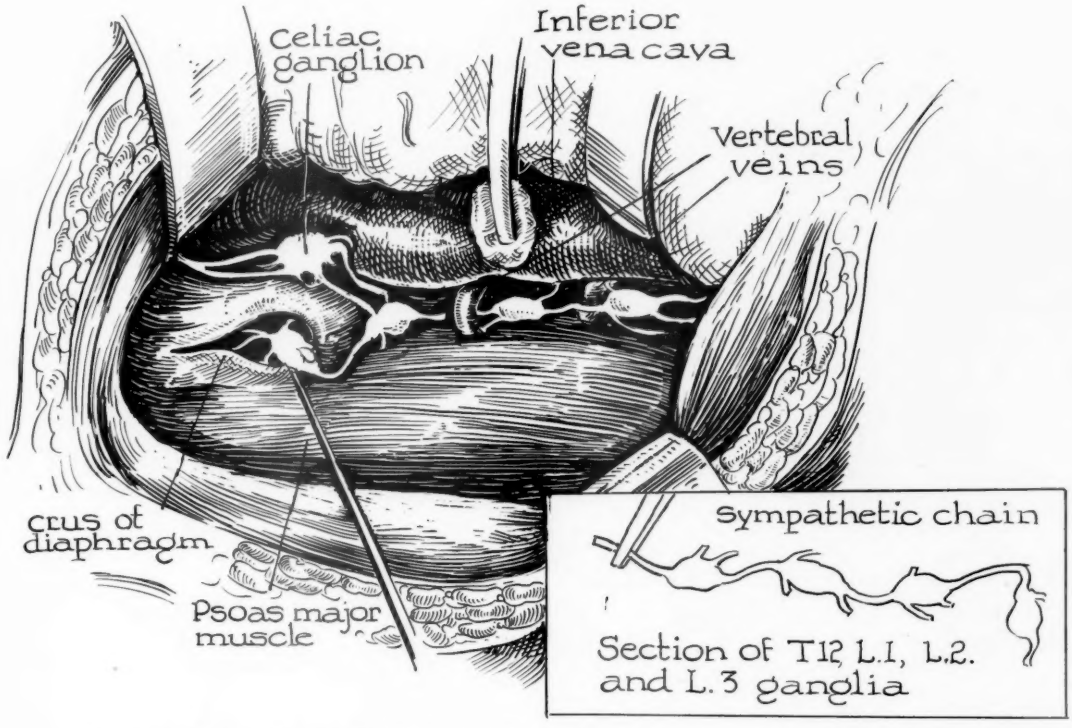

Fig. 2.—The lumbar sympathetic trunk is palpated against the vertebral bodies at the medial edge of the psoas muscle. The trunk and first, second, and third lumbar ganglia are freed under direct viualization, thereby avoiding injury to the lumbar veins which may course anterior to the trunk. The trunk is followed to the diaphragm and, if desirable, the diaphragm may be opened extrapleurally and the twelfth thoracic ganglia removed.

Yeager and Cowley[8] and Edwards[9] have emphasized the many variations which may occur in the sympathetic distribution to the extremity. Our experience has been similar to theirs. We have encountered many "double trunks" and other anomalies in which most of the sympathetic innervation of the lower extremities originated from the first or second ganglia.

Recently, Reed and Kirgis[10] have evaluated the clinical application of Cannon's law of denervation[11] and have concluded that the consideration of preganglionic versus postganglionic sympathectomy is not of value, clinically. We might point out, however, that excision of the twelfth thoracic ganglion and the first, second, and third lumbar ganglia constitutes a practical preganglionic sympathectomy.

The tendency toward regeneration of severed sympathetic pathways has been stressed by Langley[12] and many others during the past one-half century.

Without doubt, regeneration does play a part in the long-term clinical benefit of sympathectomy. We feel that regeneration can be avoided most successfully by performing an extensive sympathetic ganglionectomy, and we agree with Edwards[9] that "the removal of rather long segments of the sympathetic trunk" is advisable. Thompson, Brose, and Smithwick[13] have shown that removal of the first lumbar ganglion affords the best chance of removing existing collateral sympathetic pathways, and we feel that resection of the twelfth thoracic ganglia, with subsequent closure of the diaphragm, is the best insurance against regeneration. In regard to regeneration, we believe that most clinical failures to accomplish permanent sympathectomy of the lower extremity may be attributable to an incomplete operation, rather than to regeneration.

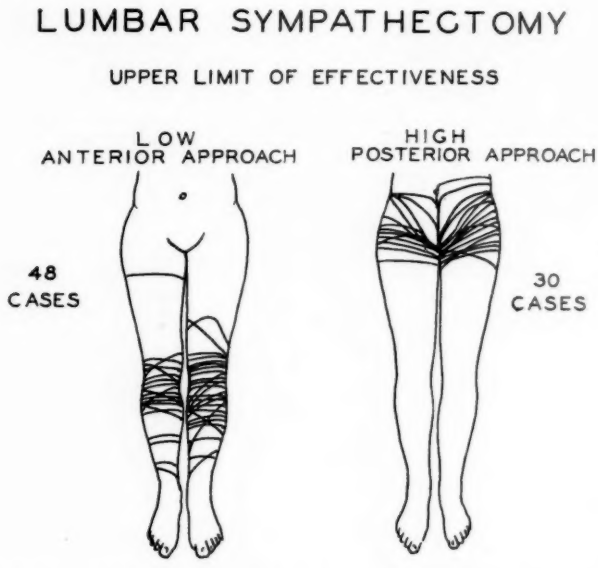

Fig. 3.—Starch-iodine studies were made on seventy-eight patients. Black lines designate lower margin of sudomotor activity, indicating a much more complete sympathectomy in those cases operated upon through a high posterior approach.

Reoperation upon those individuals who, obviously, have had inadequate sympathectomy has presented an exceedingly difficult problem when an attempt is made at exploration through the same low incision. We have encountered many such cases and have found that in them an approach through the upper part of the field is simple and safe.

One valid objection to this high operation is that simultaneous bilateral lumbar sympathectomy may be impractical where rib resection has to be carried out. We feel that it is probably better to operate on the second side at a later date, but there is no great objection to carrying out a bilateral procedure at one operation.

The question of sexual disturbances following the removal of the first lumbar ganglia may arise. Many of these individuals are in an age group in which such difficulties occur through the normal changes of senescence; for this reason, we refrain from making direct inquiry for fear of increasing the difficulties by the power of suggestion. We have had only two voluntary com-

plaints in a series of forty male patients. Alnor[14] has made a careful and scientific study of this problem, and has concluded that the age of the patient and the underlying disease which makes sympathectomy necessary play a much greater role in any impotence which may occur than does the surgical procedure.

Lindstrom[15] has reported on a series of fourteen patients in whom the classical lumbar sympathectomy failed to relieve symptoms and on whom reoperations were performed to resect the first lumbar ganglion. One-half of these were benefited, and no disturbances in sexual function were encountered.

Fig. 4.

Fig. 5.

Fig. 4 (Case A. D.).—Starch-iodine test after bilateral low lumbar sympathectomy indicating inadequate sympathectomy on left, persistence of symptoms, and failure to heal at the site of amputated digit.

Fig. 5 (Case A. D.).—Starch-iodine test following reoperation through high posterior approach indicating complete sympathectomy and healing of amputated stump.

Starch-iodine tests were carried out on seventy-eight of our patients to evaluate the effectiveness of the sympathectomies on a basis of sudomotor activity (Fig. 3). Very few of those operated upon through a low anterior approach showed signs of sympathetic interruption above the knee. All of those operated upon through the high posterior approach showed complete loss of sweating below the inguinal ligament, and many of these were dry up to the umbilicus.

A single case is presented as being a typical illustration of the results obtained in our series.

CASE REPORT

A. D., a 47-year-old white man, developed symptoms of thromboangiitis obliterans in 1950. Because of multiple gangrenous digits and painful ischemia, quadrilateral sympathectomies were performed, elsewhere, in May, 1951. The patient was relieved of symptoms until April, 1952, when he was admitted to the Surgical Service of the Veterans Administration Hospital in Coral Gables, Fla., with gangrene of the left great toe. This digit was amputated on June 4, 1952, but the operative area did not heal and pain persisted. The patient insisted on holding the foot in a dependent position, which caused edema.

A starch-iodine test (Fig. 4) revealed sweating on the medial aspect of the left leg. It was felt that reoperation for high left lumbar sympathectomy would be beneficial. This was performed on Aug. 6, 1952. The twelfth thoracic and the first and second lumbar ganglia were removed. Postoperatively there was immediate relief of pain, with obvious warming of the foot. Healing of the previous amputation site was complete within two weeks (Fig. 5). The patient is working and is free of complaints.

In an attempt to evaluate the results of a lumbar sympathectomy, we have reviewed all lumbar sympathectomies performed on patients with arterial circulatory insufficiency at the Jackson Memorial Hospital in Miami and the Veterans Administration Hospital in Coral Gables, Fla., during a four-year period ending Dec. 31, 1952.

Material Studied (Table I).—A total of eighty-five patients were operated upon one hundred fifteen times. Forty of these were in the Veterans Administration Hospital and forty-five were in the Jackson Hospital. Seventy-two of these could be located for review. There were no operative or postoperative deaths in this series, and there were no serious complications as the result of sympathectomy. Twenty-one had died of unrelated causes. Fifty-one were interviewed and evaluated.

TABLE I. MATERIAL REVIEWED

	VETERAN'S ADMINISTRATION HOSPITAL	JACKSON HOSPITAL	TOTAL
Total patients	40	45	85
Total operations	51	64	115
Operative deaths	0	0	0
Operative complications	0	0	0
Patients followed	31	41	72
Living	24	27	51
Dead	7	14	21
Cause of death			
Heart disease	4	4	8
Malignancy	2	3	5
Cerebral hemorrhage	1	3	4
Suicide	0	1	1
Undetermined	0	3	3

Type of Operation and Age (Table II).—Of the 115 operations, eighty-one were of the low type performed through an anterior approach and twenty-three were of the high type performed through a posterior subdiaphragmatic

approach. Eleven of these were reoperations in which the first low sympathectomy had been unsatisfactory and a second high lumbar sympathectomy was carried out. The average data on these patients are shown in Table II.

TABLE II. TYPE OF OPERATION AND AGE

	VETERANS ADMINISTRATION HOSPITAL	AVERAGE AGE (YR.)	JACKSON HOSPITAL	AVERAGE AGE (YR.)	TOTAL
Classical (low anterior approach)	31	48	50	57	81
Complete (high posterior approach)	10	51	13	60	23
Reoperation, first low, second high	3	39	8	54	11

Type of Disease (Table III).—Of the fifty-one patients operated upon, thirty-seven were diagnosed as having arteriosclerosis, and in this group twenty-one had diabetes. Twelve were diagnosed as having thromboangiitis obliterans. There was one with Leriche syndrome, and one case of traumatic vasospasm.

TABLE III. TYPE OF DISEASE

	VETERANS ADMINISTRATION HOSPITAL	JACKSON HOSPITAL	TOTAL
Arteriosclerosis	17	20	37
With diabetes	8	13	21
Thromboangiitis obliterans	6	6	12
Leriche syndrome	1	0	1
Traumatic vasospasm	0	1	1

Results in Living Patients (Table IV).—Sixty-eight operations were evaluated in the cases of those living patients who were located. There were fifty low lumbar sympathectomies in this group; 54 per cent showed improvement. Sixteen per cent were unimproved and 30 per cent experienced questionable results. There were eighteen high lumbar sympathectomies. Seventy-eight per cent were improved, 17 per cent were unimproved, and in one case there was a questionable result. Nine high reoperations were performed on individuals who had been operated upon through a low anterior approach, either by us or elsewhere, with unsatisfactory results. Eighty-nine per cent of these experienced improvement. The remaining eleven per cent experienced equivocal results.

TABLE IV. RESULTS OF SYMPATHECTOMY IN LIVING PATIENTS

	LOW		HIGH		REOPERATION HIGH	
Improved	27	(54%)	14	(78%)	8	(89%)
Unimproved	8	(16%)	3	(17%)	0	
Equivocal	15	(30%)	1	(5%)	1	(11%)
Total	50		18		9	
Dead	31		4		2	

CONCLUSIONS

1. Complete sympathectomy affords a practical method for improving arterial circulation to the lower extremity.

2. It is impractical, and often impossible, to attempt complete lumbar sympathectomy through the usual anterior incision.

3. Removal of the twelfth thoracic and the upper three lumbar sympathetic ganglia through a posterior subdiaphragmatic incision is a simple and safe method of accomplishing a complete sympathetic interruption to the lower extremity.

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PULMONARY VALVULOTOMY

Results of Operation in Twenty-Five Cases

George H. Humphreys, II, M.D., Samuel Powers, M.D., Hugh Fitzpatrick, M.D., and Ben Marr Lanman, M.D., New York, N. Y.

(From the Department of Surgery, College of Physicians and Surgeons, Columbia University, and the Surgical Services of the Babies and Presbyterian Hospitals)

SINCE the first introduction by Brock[1] of an operative procedure designed to overcome pulmonary valvular obstruction and since its further development by Brock[2, 3] and Blalock,[4] pulmonary valvulotomy has become established as a successful method. Refinements of technique have since been added by Potts and his co-workers,[5] but the sound physiologic principle of direct surgical relief of obstruction to blood flow into the lungs remains unaltered. There is still, however, a good deal of uncertainty as to how widely this technique can be applied to the various cardiac anomalies which include an element of pulmonic stenosis[6] and as to what results can be expected, both clinically and physiologically. Because the method is relatively new, and few series have been reported which include follow-up data,[7, 8] it seems worth while to present results of studies in a group of twenty-five consecutive patients operated upon at the Columbia-Presbyterian Medical Center between June, 1950, and December, 1952. In observing the results of operation we have attempted to determine the effectiveness of valvulotomy in producing changes in the circulation of patients with various closely related anomalies and to evaluate the clinical effects of these changes.

The group is limited to those cases in which a stenosis at the pulmonary valve was found at operation and in which incision and dilatation according to the Brock technique[3] were carried out. The age of the patient at operation varied from 4 months to 24 years, with twelve (or about one-half) in the age group between 6 and 10 years. The patients were equally divided between both sexes (Tables I and II).

Table I. Sex

	MALE	FEMALE	TOTAL
Valvular stenosis only	5	4	9
With auricular defect	2	3	5
With ventricular defect	5	6	11
Totals	12	13	25

Of the twenty-five patients, in nine (36 per cent), the anomaly was limited to the stenotic pulmonary valve. In seven of these, the valve was symmetrically stenosed into a conical diaphragm with narrowed central orifice

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through which a strong jet of blood could be felt to flow during systole. In two, the valve was irregularly and asymmetrically stenosed. In all, the pulmonary artery showed poststenotic dilatation, twice described as "aneurysmal" but, in one, this was not apparent on frontal roentgenogram.

TABLE II. AGE (YEARS)

	0-5	6-10	11-15	16-20	21-25	TOTAL
Valvular stenosis only	0	4	1	3	1	9
With auricular defect	1	3	0	1	0	5
With ventricular defect	3	5	2	0	1	11
Totals	4	12	3	4	2	25

In five patients (20 per cent) with valvular stenosis there was, in addition, a defect in the interauricular septum. In three of these, the valve was symmetrically stenosed as in the cases without other anomaly and, in two, it was asymmetrical and irregular. All showed poststenotic dilatation of the pulmonary artery at operation, but this was evident on roentgenogram in only three.

In eleven patients (44 per cent) the pulmonary valvular stenosis was combined with an interventricular septal defect and varying degrees of dextroposition or overriding of the aorta. In one patient, the aortic arch and descending aorta lay on the right, and in one there was a true dextrocardia. These patients represent a variety of tetralogy of Fallot but vary widely within the group between a situation almost indistinguishable from the first group to one practically identical with tetralogy with infundibular stenosis. In only four was there a typical conical valvular stenosis, and in only three was a poststenotic dilatation of the pulmonary artery present. The single death in the entire series was in this group (Table III).

TABLE III

	VALVE		PULMONARY ARTERY		
	CONICAL	IRREGULAR	DILATED	NORMAL OR SMALL	TOTAL
Valvular stenosis only	7	2	9	0	9
With auricular defect	3	2	5	0	5
With ventricular defect	5	6	3	8	11
Totals	15	10	17	8	25

A variety of studies were carried out on these patients before, during, and after operation. These were designed to demonstrate the circulatory abnormality not only in order to determine the anatomic anomaly, but also to define the degree of physiologic disturbance and the extent to which the procedure succeeded in restoring a more nearly normal situation. More information was obtained by catheterization studies than by any other method. Venous catheterization of the right heart by the method of Cournand and associates[9] was successful in fourteen cases.* The findings are in agreement with previous studies reported by others.[10-12]

*These studies were carried out in the cardiorespiratory laboratory of the Department of Medicine at the College of Physicians and Surgeons by Dr. John West and his associates.

In addition, direct catheterization of the right ventricle and pulmonary artery before and immediately after valvulotomy, as described by Fitzpatrick and associates,[13] was carried out in ten cases, in seven of which venous catheterization had either failed or had not been attempted. This method permits pressure recordings which correlate well with the first, but does not permit sampling for blood gas analysis. Thus, preoperative right ventricular pressure records are available in twenty-one of the twenty-five cases. Immediate postvalvulotomy pressures are available in nine, and venous catheterization has been carried out at periods up to two years after operation in four. It is unfortunate that the reluctance of parents to consent to postoperative studies once their child has been relieved of symptoms has hampered the obtaining of adequate late studies.

In addition to catheterization, radioactive isotope flow studies by the method of Powers and co-workers[14] have yielded valuable information. By this method it has been found possible not only to obtain a curve quite characteristic of pulmonary stenosis, but also to determine in many instances the direction and degree of intracardiac shunting. In some cases, small shunts were demonstrated by this method which could not otherwise be detected and which proved to be present at operation. Shifts in direction of shunting following vulvulotomy were also well shown.

VALVULAR STENOSIS WITHOUT SEPTAL DEFECT

In eight of the nine cases, catheterization studies were obtained before valvulotomy. The ninth case involved a patient whose true anomaly was not recognized before operation, since it had been mistakenly thought that he had a patent ductus arteriosus. Four of the nine were catheterized before operation. Two patients were catheterized both before and during operation, the resulting readings correlating well. Two were catheterized on the operating table immediately before valvulotomy and again immediately thereafter, without preoperative catheterization. The striking finding in this group was the high right ventricular systolic pressure, averaging 125 mm. including one reading of 32 mm. which seemed inconsistent with the patient's clinical handicap and subsequent improvement. The highest individual reading (217/9) was also in this group (Table IV).

Six patients were catheterized after valvulotomy: four, immediately; one, one year later; and one, two years later. Striking falls in right ventricular

TABLE IV. RIGHT VENTRICULAR PRESSURES BEFORE AND AFTER VALVULOTOMY: PURE VALVULAR STENOSIS

PATIENT	BEFORE	AFTER	RESULT	FOLLOW-UP PERIOD
L. C.	147/19, 149/0*	65/0*	+++	1½ yr.
R. E.	217/9	69/2	++++	1 yr.
W. F.	32/6		+++	2½ yr.
L. G.	195/8		++++	3 yr.
J. K.	92/6*	60/0*	++++	2 yr.
T. M.	104/2*	58/8*	++++	2¾ yr.
J. R.	162/12	78/15	++++	2½ yr.
A. S.			+++	1 yr.
A. S.	94/10, 85/10*	40/8*	+	6 mo.

*Direct catheterization at operation.

systolic pressure were noted in all cases, although in every case a pressure slightly in excess of accepted normal persisted. In the case studied two years after valvulotomy (J. R.) the pressure remains substantially below the preoperative level. The average was 61 mm.

The tracings, especially those obtained on the operating table, also showed striking returns toward normal, not only in the mean pulmonary arterial pressure, but also in the pulse contour, which changed from a low, damped curve to one with characteristic dicrotic notch, demonstrating restoration of valvular function (Figs. 1 and 3).

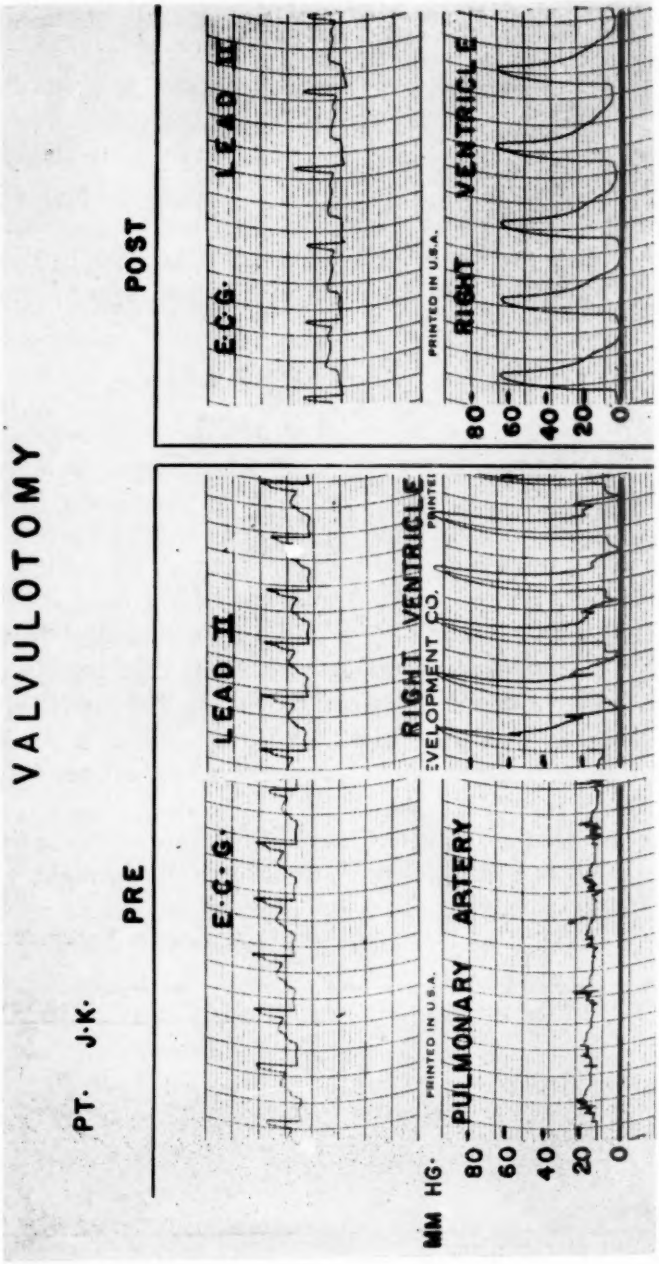


Fig. 1.—Tracings obtained by direct cardiac catheterization at operation on a patient with isolated pulmonary valvular stenosis (J. K.).

The upper tracing is a Lead II electrocardiographic record. The lower tracing shows on the left the low, damped pulmonary artery pressure contrasting with the high right ventricular pressure before valvulotomy. On the right the ventricular pressure is shown to be substantially lower immediately after valvulotomy.

Isotope dilution curves showed a characteristic slow rise in the wave, presumably due to the eddying beyond the jet of blood, which holds some of the isotope in the dilated pulmonary artery causing greater dilution. This effect has also been well demonstrated in angiocardiograms (Fig. 2).

Clinically, all of these patients showed a characteristic picture. Dyspnea was the chief complaint and varied from mild to severe. None showed cyanosis, and only one was physically retarded, a condition possibly related to concomitant bilateral cryptorchidism. In age, the patients ranged between 5½ and 24 years, the average being 13. This is distinctly older than the other groups, probably because of the absence of cyanosis and the relatively milder handicap of dyspnea only. None had shown evidence of failure.

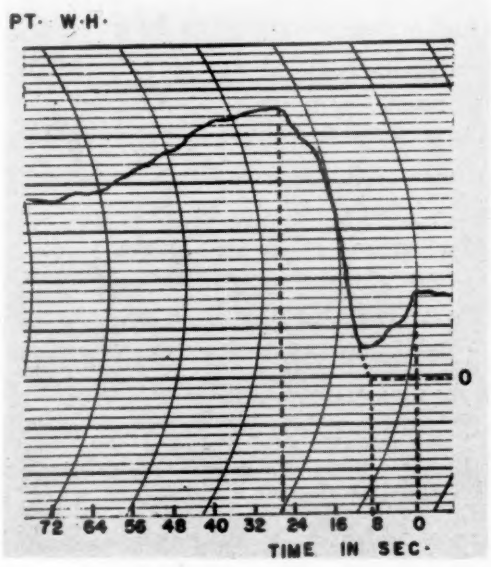


Fig. 2.—A typical curve of isotope dilution obtained in a patient with isolated pulmonary valvular stenosis (W. H.). From the injection point, *O*, on the right end of the record, the dye appears in normal time, 8 seconds (showing no right-to-left shunt). The rise to a peak at twenty-five seconds is approximately twice normal (showing delay in the passage of dye through the stenotic pulmonary valve).

Nevertheless, all but one (the most recent) were markedly improved following operation, five being able to carry out entirely normal activities and three being restricted only on vigorous exertion. However, the murmur persists with varying degrees of softening in all cases and, in all, the roentgen evidence of pulmonary artery dilatation is not noticeably changed.

VALVULAR STENOSIS WITH AURICULAR SEPTAL DEFECT

In four of the five cases, catheterization studies were obtained before valvulotomy. Two patients were successfully studied before operation; in two, attempted preoperative catheterization was technically unsuccessful; in one, a very sick infant of 4 months, it was not considered wise to attempt it. Catheterization on the operating table was performed both before and immediately after operation in two of the three patients in whom preoperative studies were not obtained and in one of the other two. The high average

right ventricular pressure (125 mm.) corresponds to that found in valvular stenosis without septal defect. In one instance, the pressure was over 200. In this child (B. C.), the valve opening was so small that the catheter occluded it, with a resultant alarming increase in cyanosis (Table V).

TABLE V. RIGHT VENTRICULAR PRESSURES BEFORE AND AFTER VALVULOTOMY: VALVULAR STENOSIS WITH AURICULAR SEPTAL DEFECT

PATIENT	BEFORE	AFTER	RESULT	FOLLOW-UP PERIOD
B. C.	201/16	77/13	++++	2½ yr.
C. M.			++	1 yr.
D. P.	122/4, 120/10*	65/10*	?	9 mo.
C. R.	125/10*	60/8*	+++	1 yr.
G. T.	100/0*	40/0,* 77/4	++++	1½ yr.

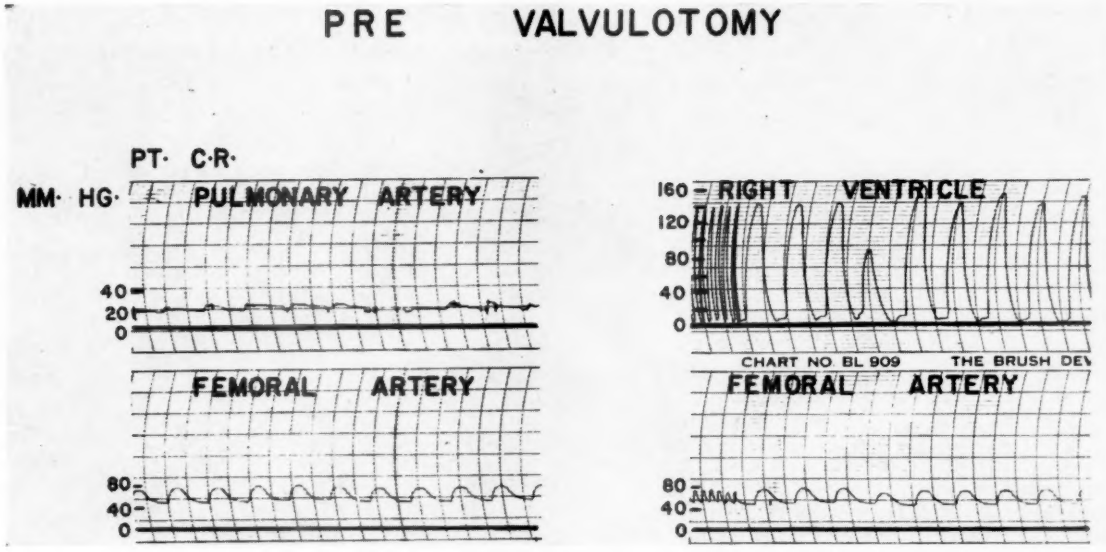
*Direct catheterization at operation.

Four of the five patients were catheterized after valvulotomy, four immediately, one six months later, and one a year and one-half after operation. In one patient (C. R.), pressure tracings taken immediately after valvulotomy indicated an inadequate fall in ventricular pressure. A second dilatation of the pulmonary valve was then performed, after which the ventricular pressure fell to a satisfactory level, with corresponding improvement in the pulmonary artery pressure curve. This case demonstrates the usefulness of immediate studies after valvulotomy and the possibility that persistent elevations of ventricular pressures found in postoperative studies may represent a technically inadequate operation rather than recurrence of stenosis. In another patient (G. T.), comparison of the immediate with the later postoperative result is possible and shows only a slight late rise in ventricular systolic pressure, to a level corresponding to that found postoperatively in cases of valvular stenosis without septal defect.

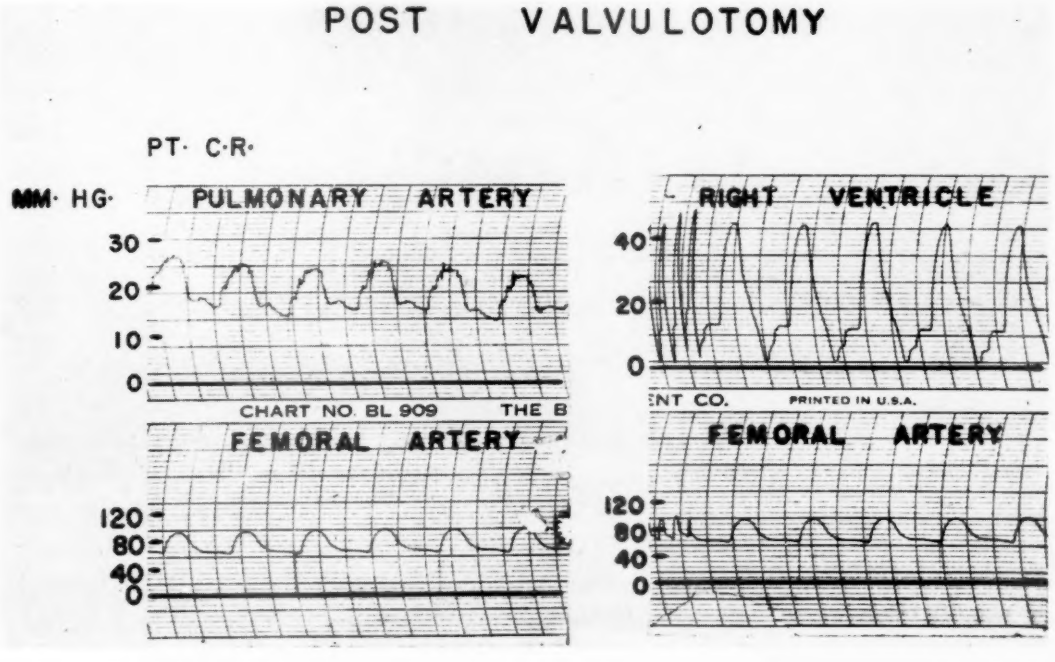
As in the previous group, the pressure curves obtained in this group postoperatively show a striking return toward normal. It is to be expected that these two groups should show similar findings, since the right ventricle, in the absence of tricuspid insufficiency, can empty only through the stenotic valve (Fig. 3).

The isotope dilution curve in this group, however, contrasts with that in isolated valvular stenosis, because of the shunting of blood across the auricular septum. Before valvulotomy, this shunt is both from right to left and from left to right, presumably varying with the phase of the cardiac cycle. The magnitude of each varies with the degree of pulmonic stenosis. After valvulotomy, the change in direction to a predominantly left-to-right shunt is well shown on these curves, which also permit an estimate of its volume (Fig. 4).

Angiocardiograms have not been successful in distinguishing these patients from those with valvular stenosis only. Presumably the shunt from the right auricle to the left is, in most cases, too small in volume to permit early appearance of contrast medium in the left heart. Prolonged visualization of the pulmonary artery is present in both.



A.



B.

Fig. 3.—*A*, Tracings obtained by direct cardiac catheterization at operation on a patient with pulmonary valvular stenosis and interauricular septal defect (C. R.). These are substantially the same as those in isolated pulmonary stenosis (Fig. 1). A low damped pulmonary arterial pressure on the left contrasts with the high right ventricular pressure on the right.

B, Tracings obtained immediately after valvulotomy on the same patient (C. R.). The rise in pulmonary arterial pressure and restoration to normal contour with dichrotic notch (indicating restoration of valve function) as well as the marked lowering of ventricular pressure are evident.

Clinically, this group of patients showed a more variable picture than the first. Cyanosis was present on exertion in three of the five, one to a very slight degree, one to an obvious degree, and in one it became progressively more conspicuous with age, being moderate even at rest at the time of operation. In the latter two, mild polycythemia and clubbing were present. In the other two cases, cyanosis was not noted, but one of these was a swarthy 4-month-old infant in whom it may have been overlooked. Dyspnea was moderate to severe in all, and two showed marked retardation in development. In age, the group was widely scattered. Only the infant showed evidence of failure.

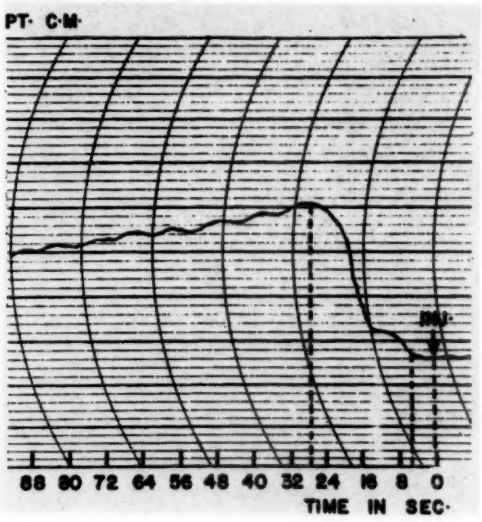


Fig. 4.—Isotope dilution curve obtained in a patient (C. M.) with pulmonary valvular stenosis associated with interauricular septal defect. Evidence of right-to-left shunt is shown by the short period of five seconds after injection at which dye first appears, although the major peak is delayed to twenty-six seconds. Evidence of left-to-right shunt is shown by the early secondary peak after the major peak, indicating recirculation through the lungs.

The operation was successful in eliminating cyanosis in all cases in which it had been present. Two patients were restored to essentially normal exercise tolerance and a third shows only slightly more dyspnea on exertion than normal. The infant, whose auricular defect is presumably large, has shown no further evidence of failure but is still markedly retarded both physically and mentally. The fifth patient developed rheumatic fever six months after operation, so the result is questionable. Murmurs persist in all, with less change than was noted in the group without septal defect.

VALVULAR STENOSIS WITH VENTRICULAR SEPTAL DEFECT

In nine of the eleven cases catheterization studies were obtained before valvulotomy. In one, catheterization was unsuccessful, and in the other, catheterization was not performed because the patient was thought to have a classical case of tetralogy of Fallot, the valvular stenosis being found at operation. Five were catheterized before operation, two both before and during

operation and two at operation only. The characteristic feature in this group was the finding of right ventricular pressures at or below the systemic arterial level, whereas in the two previous groups it frequently exceeded aortic pressure. The average was only 92 mm. In only three were postoperative readings obtained, and these demonstrated a less striking fall in pressure than in the previous groups, a finding to be expected since the ventricular defect permits the left ventricular pressure to be transmitted to the right (Table VI).

TABLE VI. RIGHT VENTRICULAR PRESSURES BEFORE AND AFTER VALVULOTOMY: VALVULAR STENOSIS WITH VENTRICULAR SEPTAL DEFECT

PATIENT	BEFORE	AFTER	RESULT	FOLLOW-UP PERIOD
J. A.	105/5, 110/0*	90/20*	++	1½ yr.
J. B.	67/8, 68/0*	40/0*	++++	1½ yr.
R. C.	114/11		+	2 yr.
S. C.	–		Died	
I. DeR.	–		++	8 mo.
B. K.	128/8		++++	2½ yr.
S. P.	98/7		±	2½ yr.
L. R.	50/0*		±	1½ yr.
R. S.	88/0*	65/0*	++	1 yr.
F. S.	90/9		+	6 mo.
R. S.	75/2		+++	2½ yr.

*Direct catheterization at operation.

The pressure tracings varied with the anatomic variation of the anomalies. Where the defect was small and overriding of the aorta was not present, they took a form similar to that seen with isolated pulmonary stenosis before valvulotomy, but the return toward normal was not as striking postoperatively because of the persistent ventricular hypertension (Fig. 5). Where the anomaly included overriding of the aorta while the pulmonary artery curve took on a more nearly normal form, the right ventricular curve was scarcely altered. Some apprehension was felt, in such cases, that the result might lead to an actual pulmonary arterial hypertension with resultant conversion to a form of Eisenmenger's syndrome, and vigorous stretching of the pulmonic ring was, therefore, not carried out.

As in the group with auricular septal defects, intracardiac shunting of blood both in direction and volume is directly reflected in the isotope dilution curves. For this reason these curves demonstrate well the variations in anatomy of the anomaly. Where no aortic overriding is present, right and left ventricular pressures may be so well balanced that the shunt is negligible before operation and the presence of a small ventricular defect may go undetected even on gas analysis of the right ventricular outflow tract blood. Yet a small early secondary peek in the isotope curve will suggest re-entry of the left ventricular blood into the lesser circulation well before the normal secondary rise of systemic recirculation. After valvulotomy, this peak is more obvious, as the ventricular pressure balance is altered and a larger left-to-right shunt occurs (Fig. 6). On the other hand, with aortic overriding and consequent entrance of right ventricular blood into the aorta, the early peak in the isotope curve will demonstrate its presence and extent; after valvulot-

omy this peak may disappear almost completely as the shunt becomes predominantly left to right (Fig. 7). The curve is not helpful, however, in distinguishing this group from classical tetralogy with infundibular stenosis. Similarly, angiocardiograms may demonstrate early aortic filling in this group but will rarely demonstrate the site of obstruction to pulmonary flow.

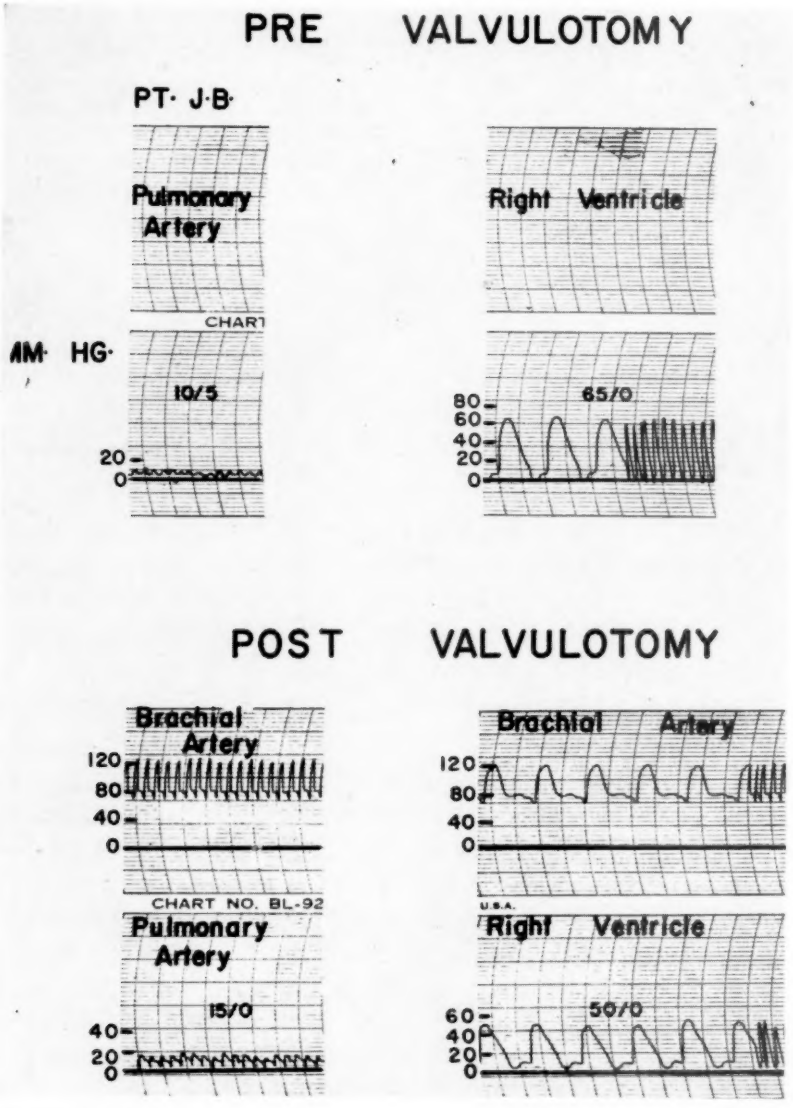


Fig. 5.—Tracings obtained by ventricular catheterization before and immediately after valvulotomy in a patient (J. B.) with pulmonary valvular stenosis and associated ventricular septal defect, but little or no overriding. The pulmonary artery tracing has improved but the right ventricular pressure, which was not excessively high even before valvulotomy, has not changed significantly.

Clinically, this is an interesting but often disappointing group. It is extremely variable. In only one patient (J. B.), whose defect was so small that it was detected only by isotope curve and proved to be present at operation, was there no cyanosis at any time. On the other hand, only two of the re-

maining ten were cyanotic from birth. Three developed cyanosis during the first year of life, and in five it appeared after the first year. In all ten, cyanosis became increasingly severe with age but in one-half of these, it was apparent only on exertion. While the other five showed some cyanosis even at rest, only one (S. P.) was constantly deeply cyanotic, and he had a complex anomaly with dextrocardia and a high degree of overriding of the aorta. As

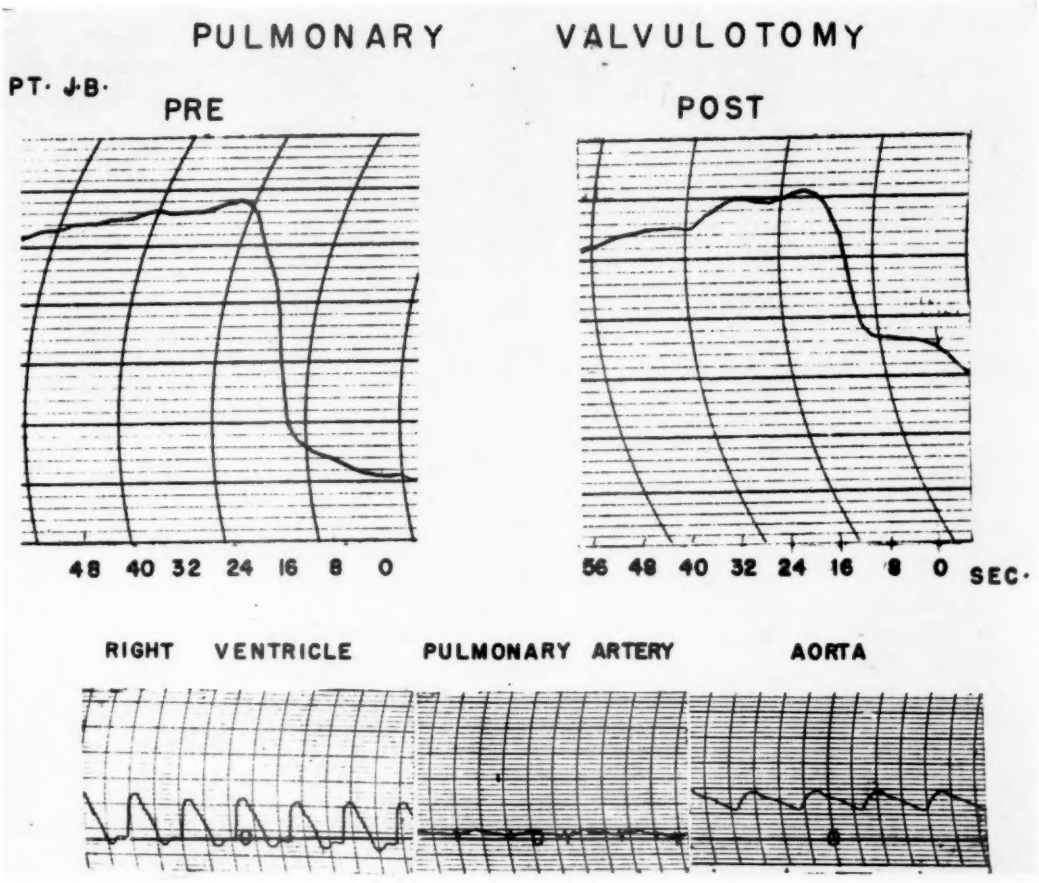


Fig. 6.—Isotope dilution curves in patient (J. B.) with pulmonary valvular stenosis and associated ventricular septal defect, unsuspected until this tracing was obtained. A small early secondary peak in the curve before valvulotomy indicates a left-to-right shunt. Immediately after valvulotomy this secondary peak is much more conspicuous, indicating considerable increase in volume of the same shunt, following relief of obstruction at the pulmonary valve.

Below are shown pressure curves on the same patient from right ventricle, pulmonary artery, and aorta, into which the catheter passed from the right ventricle, thus proving directly the presence of an interventricular defect.

would be expected, moderate clubbing of the fingers was present in three of the five who were cyanotic at rest, and slight clubbing in the other two, whereas clubbing was present in only two of the five who showed cyanosis only on exertion. The habit of assuming a squatting position was usual, being present in all but two of the cyanotic group. In these two, significant cyanosis was late in appearing.

Other evidences of congenital somatic inadequacy were also more frequent in this group. One was severely retarded physically, one was mentally defective although normal in development, and one was retarded both mentally and physically. A right aortic arch was present in one, dextrocardia in another, a left vena cava in a third, and one had an associated imperforate anus. The patient who died was found at autopsy to have also an infundibular stenosis and a patent foramen ovale.

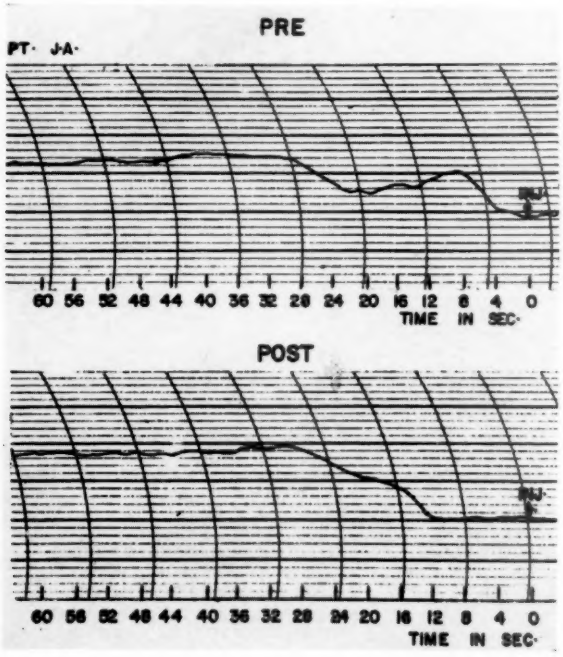


Fig. 7.—Isotope dilution curves in a patient (J. A.) with pulmonary valvular stenosis associated with ventricular septal defect and overriding aorta. The top curve, before valvulotomy, shows an early sharp peak of considerable magnitude, indicating a significant right-to-left shunt. The bottom curve, immediately after valvulotomy, shows that this shunt has been almost completely eliminated. Both curves show the early secondary peaks which indicate the rapid recirculation of left-to-right shunting.

As would be expected in such a variable group, the result of operation has been inconstant. One patient (B. K.), a woman of 23 years who had been cyanotic since birth with progression to severe exercise restriction, now shows no cyanosis and has normal exercise tolerance. One other patient (R. S.) is no longer cyanotic but occasionally squats when tired. The other seven surviving patients who were cyanotic still show some cyanosis on exertion and in two of these, there is no appreciable change. The patient without cyanosis before operation (J. B.), on the other hand, has had an excellent result comparable to the patient with valvular stenosis alone. The single operative mortality occurred in this group in a cyanotic child (S. C.) thought to have classical tetralogy of Fallot. An operation was performed one year before his death with the intention of creating a surgical ductus arteriosus, but his condition became alarming when the pulmonary artery was temporarily occluded, and the operation was terminated. One year later, on a second attempt, a

conical value and jet were found to be present and a valvulotomy was performed. At the close of the procedure, ventricular fibrillation occurred. At autopsy both a valvular and infundibular stenosis were found, as well as a patent foramen ovale. It seems probable that creation of a surgical ductus would have been a more suitable choice in this case, in spite of the failure on the first attempt.

SUMMARY

The results of physiologic studies on twenty-five consecutive cases of valvular stenosis treated by valvulotomy according to the technique of Brock are presented. Some significant findings on catheterization before, during, and after operation are presented, as well as selected examples of isotope dilution curves to demonstrate the usefulness of that method in such cases. Twenty-one of the twenty-five were catheterized before valvulotomy, and thirteen after the procedure. In nine patients, the anomaly was limited to the pulmonary valve, and in all but one of these, clinical results have been excellent. In five patients, a defect in the auricular septum was also present. Clinical results are excellent in two, good in two, and questionable in the other one. In eleven patients, a defect in the ventricular septum was also present. Reasons for the variable results in this group, which includes the only operative mortality, are discussed.

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CARDIAC OUTPUT: A CLINICAL COMPARISON OF THE DIRECT FICK, DYE, AND BALLISTOCARDIOGRAPHIC METHODS*

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THE accurate measurement of cardiac output has wide applicability in the field of vascular surgery. For this reason we have examined three of the methods in current use with a view to assessing the relative accuracy and clinical usefulness of the several methods. It has seemed particularly important to check the accuracy of the dye method. In the most seriously ill patients, the ballistocardiographic record is often so abnormal as to preclude interpretation, and in certain other patients the arms may not be available for the introduction of the cardiac catheter to obtain samples of mixed venous blood from the pulmonary artery for the direct Fick measurements.

The Direct Fick Method.—In 1870, Fick[1] proposed the principle that the rate of blood flow through an organ could be determined by measuring the arteriovenous difference of a metabolite and by measuring the amount of the metabolite consumed over a definite period of time. Grehant[2] later applied the Fick principle to the measurement of cardiac output in dogs. Forssmann[3] in 1928, in a series of experiments on himself, was the first to catheterize the right heart in man, and in recent years Cournand[4] and his associates have developed this technique to an extent which has made the direct Fick method applicable in man.

The direct Fick method suffers from certain disadvantages, however. To measure cardiac output by this method, it is necessary to cut down on a vein in the antecubital fossa. This obviously limits the number of separate catheterizations which can be accomplished in any one patient, and in certain patients the antecubital fossae may not be available. Moreover, there are occasions when the catheterization is unsuccessful, and in other instances it is inconvenient, if not clinically inadvisable, to remove the seriously ill patient to the fluoroscopic room for the catheterization procedure. Therefore, although the direct Fick method is often accepted as possibly the most accurate method available, it has its limitations.

The Ballistocardiographic Method.—As early as 1905, Henderson[5] realized that the ballistic impulses of the human body were somehow related to cardiac

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output, as he observed that breath-holding reduced the magnitude of the impulses recorded by his machine. In 1939, Starr[6] developed the ballistocardiograph to a point of clinical usefulness and derived a formula relating the magnitude of the impulses to stroke volume. The Starr ballistocardiograph is the one used in the present study.

Without entering into the controversy regarding the value of the ballistocardiographic method in patients who are not critically ill, we merely wish to restate a fact which is accepted by all workers, namely, that in the most critically ill patients, in whom cardiac output data would be most desirable, the ballistocardiographic complexes are frequently so abnormal as to preclude accurate interpretation. Particularly is this true in the severely burned patient. Therefore, while the ballistocardiographic method does permit rapid and repeated measurements in the same normal subject, in the abnormal subject this method is often not applicable.

The Blue Dye Method.—Disappointed with the limitations of first the Fick and later the ballistocardiographic methods for the study of critically ill patients, we have examined the blue dye method for the measurement of cardiac output. In 1897, Stewart[7] proposed that cardiac output could be measured if a substance were infused at a constant rate into a vein so that a concentration plateau could be achieved in the peripheral blood. He realized that the measurements had to be made before significant recirculation had taken place. It was apparent that, by knowing the amount of the substance infused per second and the concentration level of the plateau, a figure related to cardiac output could be obtained. In 1928, Hamilton,[8] while studying circulation times by the single-injection method, realized that the mean concentration of the injected substance in arterial blood was inversely related to cardiac output. Later Kinsman[9] demonstrated that following a single injection of a substance it was possible to correct for the recirculation by plotting the concentrations of timed arterial samples on semilogarithmic paper. This is essentially the method that is in use today.

To apply the dye injection principle, one can use either the kymographic method of Hamilton and associates[8] or a more elaborate automatic recording device as advocated by Friedlich, Heimbecker, and Bing.[10] It is possible to purchase parts for the manufacture of a constant-flow cuvette for approximately eighty dollars. The cost of this item, if purchased assembled, is many times this amount. Certain auxiliary parts, such as a direct current amplifier and a sensitive recording galvanometer, are required. These items are costly.

The advantages of the constant-flow cuvette are mainly those of convenience. As the blood flows through the cuvette, an automatic record is made of the light transmission through the flowing blood. Multiple records can be made, and it is not necessary to read each individual sample in a spectrophotometer as in the Hamilton method.

The disadvantages of the constant-flow cuvette are numerous. A calibration curve must be plotted for each patient and more than one for the same patient if the oxygen content of arterial blood changes. Change in the rate

of flow of blood through the cuvette influences the transmission readings; therefore, adequate precaution must be taken to insure constant flow. The apparatus is elaborate, and as much blood is shed as with the Hamilton method. For these reasons we have used the kymographic method of Hamilton.

If the dye method can be shown to have an accuracy comparable to that obtained by the use of the Fick method or the ballistocardiograph, it may become the clinical method of choice, for it offers certain advantages which the other two methods do not. Multiple measurements may be performed on the same patient without the necessity of moving the patient to the fluoroscopic room. Moreover, the method can be used in the seriously ill patients whose ballistocardiographic tracings are frequently unreadable, and it can often be used in patients who have been severely burned and whose antecubital fossae may not be available for catheterization.

PROCEDURE USED IN THE PRESENT STUDY

The patient was allowed nothing but water for eight hours preceding the study. Thirty minutes before the skin was incised for the introduction of the cardiac catheter into the antecubital vein, the patient received 0.18 Gm. of Sodium Amytal orally. The patient was then moved to the ballistocardiographic table, and a tracing was taken after fifteen minutes. Following this he was placed upon the fluoroscopic table in a quiet room where, under sterile conditions, the cardiac catheter was introduced into an antecubital vein and passed into the pulmonary artery under fluoroscopic control. The next step consisted of introducing a special indwelling needle with stylet into the femoral artery under local anesthesia for the collection of the blood samples necessary for both the Fick and dye determinations. After a five-minute period the patient was allowed to begin breathing pure oxygen through a Sanborn basal metabolism rate machine. The kymograph assembly was placed beside the patient in such a manner as to permit the polyethylene tubing to reach readily the indwelling needle in the femoral artery (Fig. 1). Ten minutes after the patient started breathing pure oxygen, the first blood sample was collected from the pulmonary artery, the second sample from the femoral artery, the third sample from the pulmonary artery, and the last sample from the femoral artery. Immediately following the collection of the direct Fick samples for arterial and venous oxygen analyses, the kymograph assembly was started by one operator. Thirty seconds later, the polyethylene tubing with Luer Lok adaptor was connected to the indwelling needle by one operator while another operator started the kymograph timer and rapidly injected 1 c.c. of 0.5 per cent blue dye (T 1824) into the indwelling intravenous needle. Forty seconds after the time of injection, the kymograph was stopped, the polyethylene tubing was disconnected, and the stylets were replaced in both the intra-arterial and the intravenous needles.

Both the dye and the Fick measurements were then repeated as soon as a second kymograph drum with mounted fresh tubes could be substituted for the one which contained arterial blood from the first dye measurement. Mean-

Fig. 1.—Measurement of cardiac output by the direct Fick, dye, and ballistocardiographic methods. This figure shows a patient lying on the ballistocardiographic table, the cardiac catheter protruding from beneath the sterile drapes covering the left arm, and the dye method in operation. The photograph was taken during a dye determination. One operator can be seen holding the polyethylene tubing that has been connected to the indwelling arterial needle. Blood can be seen flowing through the polyethylene tubing into the revolving tubes. The other operator has previously injected the blue dye into the catheter and can be seen holding the syringe containing 15 c.c. of saline solution that was injected rapidly to wash the blue dye into the pulmonary artery through the indwelling cardiac catheter. In about one-third of our cardiac output determinations the dye has been injected into the cardiac catheter and rapidly washed into the circulation with 15 c.c. of saline solution. The catheter is used for this injection when a large vein is not readily available in the other arm, which was the case with this patient. The ballistocardiographic tracing and the Fick arterial and mixed venous blood samples have already been obtained. A second series of determinations by both methods (Fick and dye) is made as rapidly as possible after the first. The oxygen consumption is measured by the Sanborn basal metabolism rate machine shown at the far right of the photograph. Normally the patient is placed upon the ballistocardiograph, a tracing is taken, and then he is moved to the fluoroscopic table, where he remains for the duration of the procedure. For the purpose of illustration, however, we have here placed the patient back upon the ballistocardiograph after the cardiac catheter has been introduced into the pulmonary artery under fluoroscopy.

TABLE I. CARDIAC OUTPUT DETERMINATIONS BY THE FICK, DYE, AND BALLISTOCARDIOGRAPHIC METHODS

PT.	SEX	AGE (YR.)	HT. (CM.)	WT. (KG.)	DIAGNOSIS	EXP. NO.	O_2 USED	A-V DIFF. VOL. %	CARDIAC OUTPUT			SURF. AREA (SQ. M.)	CARDIAC INDEX	
									FICK	DYE	BALLISTOGRAPH		FICK	DYE
W. G.	M	57	180	54.5	Ca. of rectum	1	226	5.70	3.97	4.84	3.58	1.63	2.44	2.97
R. L.	M	49	178	84.5	Inguinal hernia	1	338	4.66	7.25	5.63	7.17	2.00	3.62	2.82
J. H.	M	28	173	71.0	Burn	1	254	4.89	5.20	8.30		1.83	2.84	4.54
						2	300	5.71	5.25		7.60		2.87	
R. M. B.	F	37	165	62.7	Lipoma	1	250	4.81	5.19	4.78		1.68	3.09	2.85
						2	250	4.68	5.33		5.12		3.18	
M. J. G.	F	40	152	55.0	Nodular goiter	1	170	4.37	3.90	4.50		1.50	2.60	3.00
						2	153	3.91	3.90		5.68		2.60	
R. T.	M	18	170	77.0	Pilonidal sinus	1	280	4.74	5.90	8.10		1.87	3.25	4.33
						2	305	5.34	5.70	7.55	6.36		3.00	4.03
A. M.	F	42	162	54.1	Granuloma of vulva	1	221	3.00	7.37	6.40		1.36	5.41	4.71
						2	218	4.11	5.38	7.00			3.95	5.15
O. K.	M	46			Postoperative hernia	1	266	7.11	5.40	6.00	6.37			
L. T.	M	20			Laceration of tendon	1	300	3.83	7.83	5.22				
						2	295	3.50	8.44	5.38	7.80			
E. J.	M	24			Stab wound of thorax	1	317	3.51	9.03	8.65	6.38			
L. C.	M	57	180	81.8	Hypertension	1	217	5.84	3.72			2.00	1.86	
						2	200	5.72	3.50	4.94	3.35		1.75	2.73
A. M.	F	57	169	50.0	Ca. of esophagus	1	193	4.61	4.20	4.20		1.55	2.71	3.29
						2	205	3.99	5.20	6.00	5.30		2.71	3.87
M. W.	F	39			Lymphopathia venereum	1	171	3.35	5.10	3.80				
L. H.	M	24	158	51.4	Perirectal abscess	1	193	4.19	4.60	5.20		1.33	3.46	3.90
						2	191	4.40	4.35	5.20			3.27	3.90
C. B.	F	40	156	62.2	Hemorrhoids	1	199	6.04	3.30			1.61	2.05	
						2	206	6.05	3.40	6.43			2.15	4.00
R. T.	M	49	147	52.0	Inguinal hernia	1	197	4.43	4.44	4.50		1.43	3.10	3.14
						2	198	4.44	4.50	4.90			3.14	3.43
W. M. W.	F	44	168	60.8	Pheochromocytoma	1	190	4.17	4.55	4.97		1.68	2.71	2.96
						2	170	4.13	4.10				2.46	
E. B.	M	23	180	88.6	Hernia	1	285	3.03	9.40	8.30		2.09	4.50	3.97
						2	270	2.54	11.60	6.60			5.55	3.16
F. S.	M	20	179	82.7	Hernia	1	308	5.31	5.80	11.80		2.00	2.90	5.90
						2	330	5.03	6.50				3.25	
K. B.	F	44	168	65.5	Lipoma	1	295	3.96	7.45	8.10		1.73	4.30	4.68
						2	241	3.88	6.20	7.65			3.59	4.42
C. P.	M	24	167	70.0	Gunshot of thigh	1	338	5.06	6.70	7.33		1.78	3.76	4.12
						2	330	4.84	6.82	8.10			3.83	4.56
J. I.	M	23	185	91.0	Laceration of thigh	1	410	4.32	9.50			2.14	4.44	
						2	368	4.27	8.60	9.60			4.02	4.49

while, the patient had been breathing pure oxygen, and the oxygen consumption was measured at the time of the taking of the Fick samples.

By this technique, two measurements of cardiac output by both the Fick and the dye method were obtained in only a few minutes. The blood oxygen analyses were made by the micromethod of Roughton and Scholander,[11] which has been checked previously with the manometric procedure of Van Slyke. Normally, determinations would be thrown out if duplicate blood samples did not check within 0.2 volume per cent. In this paper, however, no determinations were thrown out because of a lack of agreement greater than 0.2 volume per cent. Further details concerning the dye method are to be reported elsewhere,[12]but basically the Steward-Hamilton technique was employed in the calculation of cardiac output by the dye method.

RESULTS

The data are shown in Table I. The numerals 1 and 2 refer to the first and second measurements, respectively, taken on each patient. The samples for the dye measurements were collected first in Patients 1 through 13, and the samples for the Fick measurements were collected first in Patients 14 through 22. The initial Fick sample, F1, and initial dye sample, D1, were collected as nearly simultaneously as possible, as were F2 and D2. Moreover, the collection of the samples for the second paired measurements (Fick and dye) followed the collection of the samples for the first pair of measurements as closely as possible. Thus, the two dye measurements and the two Fick measurements were all accomplished in only a few minutes' time, in an effort to minimize the differences due to variations in actual cardiac output.

The results of the statistical analysis, including the mean, standard deviation, and the degree of freedom, are given in Table II. Essentially, the study would seem to indicate the following points. First, in these "normal" patients the ballistocardiograph gave consistently good results and on the surface might appear to be quite useful clinically; actually, this is not the case,

TABLE II. ANALYSIS OF DATA FROM TABLE I

Cardiac Output

	FICK 1	DYE 1	FICK 2	DYE 2	BALLISTOGRAPH 2
Mean	5.75	6.22	5.99	6.81	5.88
Standard deviation (±)	1.80	2.05	2.20	1.44	1.47
Degrees of freedom	20	17	17	12	10
Coefficient of variation	.314	.331	.367	.212	.250

F = 0.723, not significant at the 5 per cent level

Cardiac Index

	FICK 1	DYE 1	FICK 2	DYE 2
Mean	3.305	3.718	3.268	3.976
Standard deviation (±)	0.947	0.955	0.903	0.687
Degrees of freedom	16	13	14	10
Coefficient of variation	0.286	0.256	0.276	0.172

F = 1.908, not significant at the 5 per cent level

since in many seriously ill patients the ballistocardiograph is unsatisfactory. Second, there is no particular advantage of the Fick method over the dye method from the point of view of accuracy (Table II). Third, both methods have a standard deviation of almost 2 L. or approximately 30 per cent. Fourth, and most important, multiple measurements with any one of the three methods, performed on the same patient at the same time, agree to within approximately 10 per cent. Since, therefore, either the dye or the Fick method is acceptable for comparing alterations of cardiac output in the same patient, the more easily performed dye method would appear to have certain advantages for clinical use.

DISCUSSION

Our results compare well with those of Hamilton and associates.[13] If variations in the body surface area of the patients are taken into consideration, both the standard deviation and the mean are diminished, as may be observed from the cardiac index in Table I, and the coefficient of variation becomes slightly less. The correlation coefficient between the Fick and the dye methods is 0.455, which is statistically significant at the 5 per cent level. The absence of a higher degree of correlation may be due to a number of factors. First, it is possible that the cardiac output actually changed in the short time which elapsed between the Fick and the dye measurements, but it is considered unlikely that a change of significant magnitude occurred. Second, the Fick method includes the measurement of the oxygen concentration in samples of venous and arterial blood and of oxygen consumption with the basal metabolism rate machine. The analytic error in the oxygen determinations is ±6 per cent, and the magnitude of the error incurred in measuring the oxygen consumption with the Sanborn machine is unknown. If a leak around the face mask should occur and remain constant, the error can be common to both the Fick measurements which were made for each patient. Third, the Fick method measures average cardiac output over a period of many minutes, whereas the dye method measures cardiac output over a period of only a few seconds. In the Fick method, brief variations in cardiac output would be "averaged out," but these variations could substantially alter the result obtained in any single dye measurement. Therefore, respiratory and other clinical physiologic variations could play a role in the observed variations in cardiac output. Fourth, if an unsuspected cardiac shunt were present, further discrepancies in the results obtained by either method could be expected.

CONCLUSIONS

1. The direct Fick, dye, and ballistocardiographic methods have been compared in eleven patients, and the first two methods have been compared in twenty-two patients.

2. Although the direct Fick method has been the "reference standard" for many years, its use in the clinic is limited.

3. The ballistocardiograph is easily the most convenient of the three methods and, in "normal" patients, the results obtained with this method

compare favorably with those obtained with the Fick. However, in severely ill patients the ballistocardiographic tracings are frequently so abnormal as to defy accurate interpretation.

4. The dye method is simple and is readily applicable clinically. It compares favorably with the Fick in accuracy, and serial (duplicate) measurements in the same individual have been found to vary less than 10 per cent. One disadvantage is that in patients with intracardiac shunts or auriculoventricular fistulas a very abnormal dye curve may be obtained.

The statistical analyses herein reported were generously performed by Dr. R. V. Brown, Department of Pharmacology, Medical College of The University of Tennessee.

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THE INFLUENCE OF ACUTE HYPERVOLEMIA ON THE FREEZE-DRY HOMOLOGOUS AORTIC GRAFT

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SEVERAL types of material have been utilized by investigators to maintain the continuity of the lumen of a major artery, a portion of which has been interrupted during development or by disease or trauma. These materials include glass tubes,[2] plastic tubing,[7] Vitallium tubes with a vein lining,[1] tubes fashioned from autologous tissue,[16, 19] segments of veins,[10] and, finally, segments of arteries.[3, 5, 6, 11, 13, 15, 17, 18, 20] Perhaps the most promising graft material tested thus far is fresh autologous artery.[9, 13, 18] This material, however, is rarely available in sufficient quantity or adequate size to be of value clinically, although short segments may sometimes be made available for use as described by Potts and associates.[18]

During recent years the use of homologous arterial grafts has been extensively studied, and a number of methods for preservation of the tissue prior to use have been investigated. Debate has centered around the question of whether viability of the graft at the time of implantation was necessary for success of the grafting operation. It has been shown that nonviable grafts preserved by the freeze-dry method have healed to the normal adjacent artery,[11, 15] and continuity of the vessel lumen has been maintained. Other studies suggest that viable cells in homologous arterial grafts preserved by other methods do not maintain viability after implantation into a host.[4, 20]

Whereas the immediate success of the homologous arterial graft is encouraging, unless some form of acute stress can be brought to bear on the implanted homografts, years may elapse before an appraisal can be made of the degenerative changes to which the graft may be susceptible. The purpose of this study is to report the results of a series of experiments in which an attempt was made to test the susceptibility of implanted arterial homografts to an acute injury. After considering several methods of stress, it was decided to attempt the production of lesions in these grafts by the administration of large infusions of lipid emulsions.

The freeze-dry method of preservation of arteries was selected because of the advantages of being able to store preserved arteries for a prolonged period at room temperature and the apparently low incidence of thrombosis after implantation in the host.[15, 21]

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METHOD

Healthy mature dogs were sacrificed and utilized as a source of aortic tissue. Sterile segments of the thoracic aorta were rapidly frozen immediately after death by dropping each section into an individual dry centrifuge bottle partially submerged in liquid air. After freezing, drying of the aortic segments was accomplished in a lyophilizer at a pressure of 0.1 to 4.0 μ of mercury. After a drying period of from thirty-six to seventy-two hours, the specimens were sealed in their glass containers at a pressure of approximately 30 μ of mercury.

Freeze-dry aortic homografts were implanted in a series of twelve normal adult dogs. A small segment of the host thoracic aorta was removed between Potts ductus clamps and a reconstituted homograft sutured in place by a continuous everting mattress suture, posteriorly, and interrupted everting mattress sutures, anteriorly. Ischemia of the spinal cord was prevented during the period of aortic occlusion by the establishment of a shunt between the proximal end of the left subclavian artery and the proximal end of the left femoral artery through a long polyethylene tube with an internal diameter of approximately 1.5 mm. (Fig. 1). Following implantation of the aortic graft, the animal was allowed to recover and was placed on standard kennel care. Approximately eight to nine weeks following implantation of the graft, one-half of the series of animals, usually alternates, were subjected to hypervolemic-lipid stress.

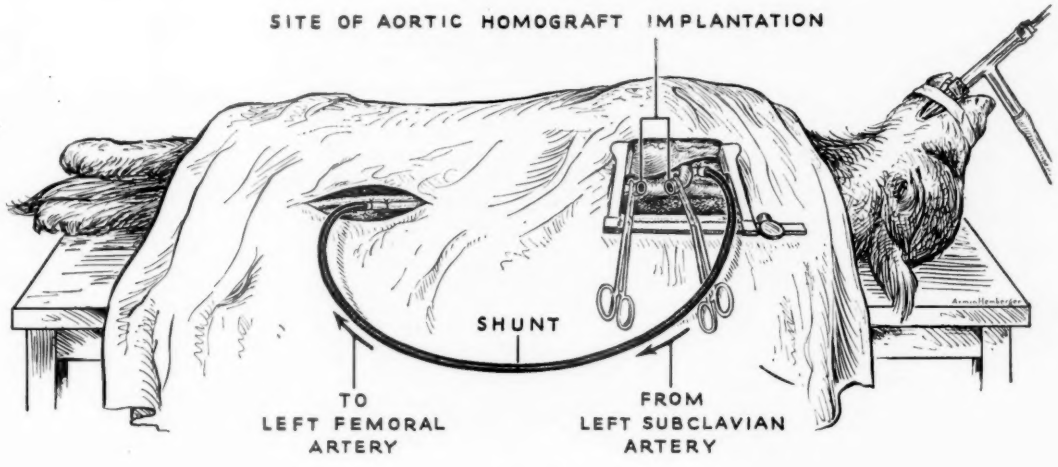


Fig. 1.

To effect the desired hypervolemia a saline emulsion of egg yolk was infused intravenously into the dogs once daily for varying periods (Table I). The egg yolk emulsion was prepared by mixing egg yolks with twice their volume of sterile normal saline solution and then filtering through sterile gauze. The total volume of each infusion was 17 c.c. per kilogram. This amount of egg yolk is usually well tolerated by normal animals and produces a marked and persistent lipemia. All fractions of blood lipids rise progressively, and by the third injection the total blood cholesterol is about 500 mg. per cent, and it usually remains at this level. Three of the six animals so treated died after

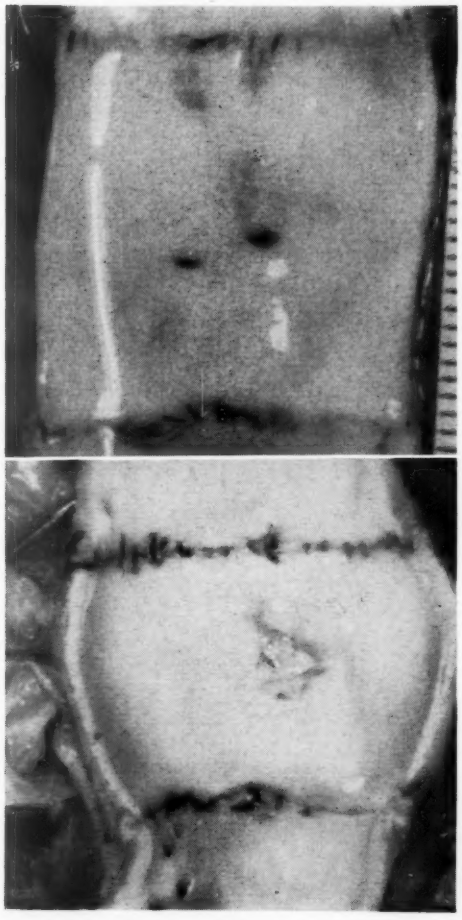
TABLE I

HOST		GRAFT			STRESS		RESULTS				
EXPERIMENT NUMBER	LENGTH OF SURVIVAL (DAYS)	DONOR	LENGTH OF PROCESSING (HOURS)	LENGTH OF STORAGE (DAYS)	NUMBER OF INFUSIONS	NUMBER OF DAYS	CALCIFICATION	HEMORRHAGE	SUBENDOTHELIAL MURAL THROMBI	FAT INFILTRATION	INFLAMMATORY AND FOAM CELLS
1	71	L–1	72	82	9	10	None	None	Present	Heavy	Many
3	78	L–4	72	44	4	8	Diffuse	None	Present	Heavy	Many
5	73	L–6	72	12	4	5	None	Medial	Present	Heavy	Many
8	76	L–7	48	32	7	11	Diffuse	None	Present	Slight	Slight
10	79	L–10	72	21	7	14	Diffuse	Intimal	Present	Heavy	Many
11	63	L–9	72	32	1	1	None	None	Present	Heavy	None
2	72	L–4	72	37			None	None	Present	None*	None*
4	28	L–6	72	5			Localized	None	Absent	None*	None*
6	78	L–7	48	18			None	None	Present	None*	None*
7	86	L–7	72	22			None	None	Present	None*	None*
9	78	L–9	36	14			None	None	Absent	None*	None*
12	56	L–10	72	56			None	None	Present	None*	None*

*Some fat, inflammatory cells, and foam cells only seen around sutures in control group.

hypervolemia was produced but before completion of the contemplated course of infusions. Three animals were sacrificed after receiving a complete course of infusions. Six animals with implanted freeze-dry aortic grafts received no stress and were sacrificed at approximately the same time following implantation as the stressed group of animals.

A.



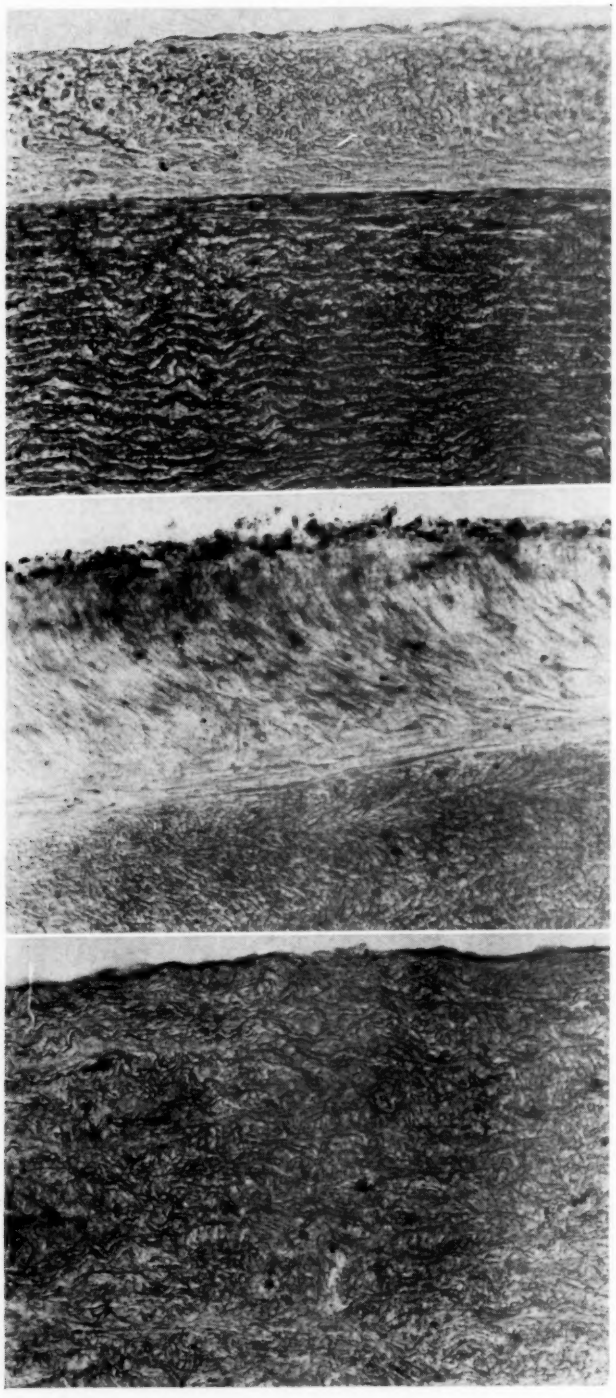
B.

Fig. 2, *A* and *B*.—Gross specimen of implanted aortic freeze-dried homografts.
A, Control group (Experiment 2), seventy-two days after implantation, showing soft, pliable graft with several small mural thrombi.
B, Control group (Experiment 3), seventy-eight days after implantation, illustrating stiffened graft due to medial calcification. Also note mural thrombus.

At necropsy the aorta was removed en bloc and fixed in 10 per cent formalin. Frozen sections of the fixed tissue were stained for fat with sudan IV. Masson's trichrome stain was also made of the same and additional blocks .

RESULTS

Despite the fact that aortic occlusion sometimes exceeded two hours while the graft was sutured in place, the small polyethylene shunts functioned well,



C.

D.

E.

Fig. 2, *C*, *D*, and *E*.—Microscopic sections.

***C*, Control group (graft of Experiment 2), note thickened intima but absence of fat, inflammatory cells, and foam cells. Sudan IV. (×285, reduced one-third.)**

***D*, Stressed group (graft of Experiment 3), illustrating a thickened intima with many subendothelial foam cells and diffuse fat infiltration of intima and inner media. Sudan IV. (×285, reduced one-third.)**

***E*. Stressed group (host aorta in Experiment 3), note diffuse but minimal fat infiltration. No foam cells were seen. Note also that intima is a single endothelial-cell layer. Sudan IV. (×285, reduced one-third.)**

and there was no evidence of paraplegia in any animal. At necropsy the implanted grafts were patent and appeared grossly and microscopically similar to other homologous aortic grafts as described by other investigators.[3, 15] A thickened intima had grown in from the host aorta covering the entire inner surface of the graft. Muscle fibers in the media had disappeared and the elastic fibers were condensed and slightly fragmented. There was evidence of ingrowth of fibroblasts and capillaries from the host into the wall of the graft. Subintimal mural thrombi were seen in all six of the grafts in the stressed group and in four of the six grafts in the control group (Fig. 2, *A* and *B*, and Fig. 3).

Several important changes not apparent in the adjacent host aorta were noted in the grafts of the stressed animals. These grafts showed a diffuse infiltration of fat with frequent foam cells and inflammatory cells, especially in the intimal layer (Fig. 2, *C* through *F*). Diffuse calcification was present in three of these grafts (Figs. 2 and 3). In addition, two grafts in the stressed group showed large areas of hemorrhage, in the medial layer in one case and in the intimal layer in the second. There was a heavy concentration of fat in each of these areas of hemorrhage. In the control group of nonstressed animals only one of the grafts showed any of these changes, this being in the form of a single plaque of calcium. A summary of these findings will be found in Table I.

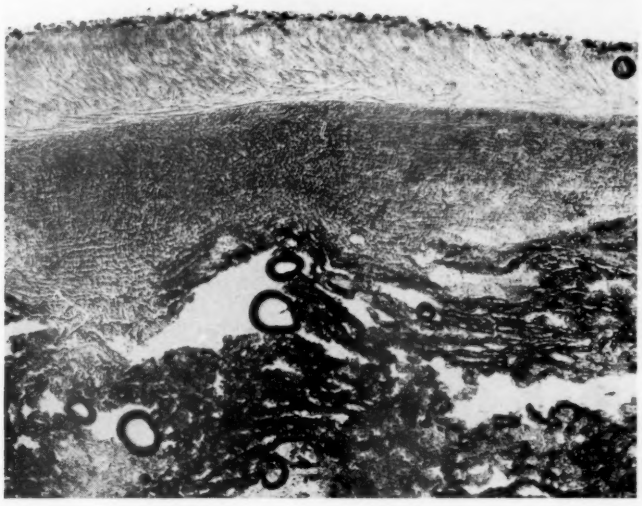


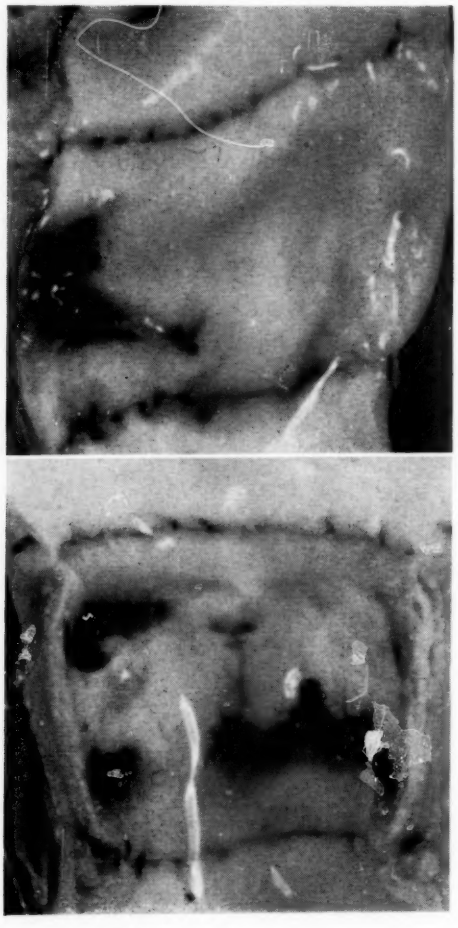
Fig. 2, *F*.—Stressed group (graft of Experiment 3), note destruction of media by calcification. Sudan IV. (×120, reduced one-third.)

DISCUSSION

There is no convincing evidence that any of the cellular elements of an arterial homograft survive or grow following implantation. As pointed out earlier, other investigators have demonstrated that viability of the graft at

the time of implantation in the host is not a requirement for success of the graft when judged by healing of the graft to the artery of the host and by the patency of the vessel lumen. From the point of view of long-term survival of a functioning graft, it is important to determine if the method of preservation will influence the eventual development of degenerative changes in the graft. There is already some evidence[8, 12] to suggest that the electron radiation method of sterilization of the graft may predispose the graft to excessive calcification. There is also evidence that a high percentage of grafts preserved by formalin

A.



B.

Fig. 3.—Gross specimens of implanted aortic freeze-dry homografts.
A, Control group (Experiment 7), eighty-six days after implantation. A subendothelial mural thrombus is seen. Graft was soft and pliable.
B, Stressed group (Experiment 8), seventy-six days after implantation. Several subendothelial mural thrombi are seen, and the walls of the graft are thickened and calcified.

fixation develop calcification after implantation.[17] On the other hand, studies using homologous arterial grafts preserved by the freeze-dry method[13, 14] and in nutrient media[4, 5] have been carried out for two years after implantation of

the grafts and have shown a low incidence of degenerative changes in the artery wall. To complete the evaluation of the influence of age on the development of degenerative changes in these grafts, however, it may be necessary to follow these animals for much longer periods.

Waters and deSuto-Nagy[23] have found that when hypervolemia is produced in dogs by the rapid infusion of compatible dog plasma, there is acute intimal injury of the aorta and coronary arteries. This injury consists of subendothelial edema and leukocytic infiltration, giving rise within a few days to a thin subendothelial scar. Waters[22] has extended these observations to the lesions that follow hypervolemia produced in dogs by the rapid intravenous injection of lipid emulsions and has found that lipid localizes in the arterial wall selectively at areas of injury. Furthermore, he has noted the similarity of site of location of these lesions to those of arteriosclerosis in man and also striking morphologic similarities between the experimental lesions and those of early arterioclerosis.

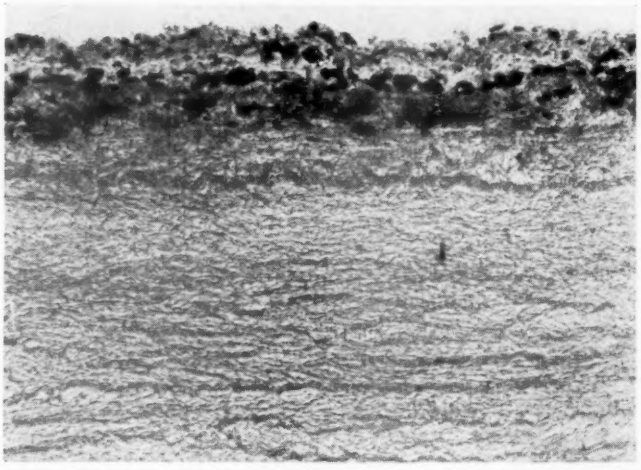


Fig. 4.—Early arteriosclerotic changes found in the aorta of an 8-year-old boy. (Accidental death.) Note fat infiltration of the thickened intima, with many foam cells. Lesion is similar to that found in stressed homograft (Fig. 2, *D*). Sudan IV. (×285, reduced one-third.)

The healed aortic homograft was considered to represent an area of lessened resistance in the aortic wall, subject throughout the life of the host to various conditions of stress. The hypervolemic stress described, combining a factor of hyperlipemia, proved to be a convenient method of testing this hypothesis. The excessive fat deposits, inflammatory cells, foam cells, hemorrhage, and calcification seen in some of these grafts following hypervolemia-lipid stress suggest that the aortic homograft preserved by the freeze-dry method is more susceptible to injury than the adjacent normal host aorta. The changes found in the wall of the grafts in the stressed group may not be progressive, but at the time of sacrifice of the animals they present many similarities to early arteriosclerotic changes in the human artery (Fig. 3). It remains to be determined whether grafts preserved by other methods are affected in a similar way by this form of stress.

The organizing mural thrombi which were observed in the implanted grafts in these experiments appeared more severe in the stressed group, although in no case did they interfere with the patency of the graft. The high incidence of these lesions in the control group of animals, higher than reported by other investigators,[11, 14, 15] suggests that what appears to be minor differences in the technique of processing of the freeze-dry graft may be responsible for these lesions.

SUMMARY

Aortic homografts preserved by the freeze-dry technique were subjected after eight to ten weeks of implantation in a host to a stress in the form of multiple infusions of an egg yolk saline mixture. All grafts so treated showed extensive infiltration with fat, foam cells, and inflammatory cells. These changes were much more marked in the graft than in the adjacent normal host aorta. Diffuse calcification of the graft was evident in one-half of the grafts in the stressed group of animals. In a control group of animals receiving no stress, fat deposits were rarely seen in the graft. Diffuse calcification and inflammatory and foam cells were not observed in the control group of grafts, although a single plaque of calcium was found in one of these grafts. The findings indicate that grafts preserved by the freeze-dry method, when subjected to appropriate stress, show changes in the vessel wall similar to those seen in degenerative arterial disease in the human being. The results of these experiments suggest that this method of stress, applied a relatively short time after implantation of the graft, may be of value in the investigation of the influence of methods of preservation on the ultimate development of the degenerative type of lesion in the wall of a grafted segment of artery.

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THE MANAGEMENT OF RECURRENT VARICOSE VEINS

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IT IS an admitted fact that there is no guaranteed long-term cure for varicose veins. However the trends of treatment are gradually producing an increasing incidence of good results. The general acceptance of the basic principle that, as a primary requisite, the great and/or small saphenous vein should be ligated and divided flush with the deep vein has produced many cures, or considerable improvement, to the unfortunate possessors of these abnormal veins. Ten years ago, the operation of high ligation, with or without multiple lower ligations and the use of sclerosing injections, was thought to be the answer to the problem. In the interval, however, the large number of recurrences which have followed this procedure have greatly shaken this opinion. Surgical opinion has now turned to other more radical measures in an attempt to produce better results. At the present time it is the consensus of opinion of the majority of vascular surgeons that the operation of flush saphenous ligation (including the small saphenous vein where indicated) with stripping of each vein to the dorsum of the foot is the procedure of choice. Again, no promise of permanent freedom from recurrence can be offered.

This presentation concerns a relatively large group of patients who have already undergone vein ligation but whose varicose veins have recurred. On examination they can readily be separated into two main categories. The first group contains those in whom the initial surgery obviously did not conform to the basic principles mentioned previously. Examples are still encountered of relatively recent surgery performed by those with little understanding of the problem, where the ligation was performed well below the groin or where the surgeon contented himself with a local excision of a mass of varices. Such cases present no problem in management. It is the second category which presents a more difficult solution where, apparently, a proper proximal ligation was carried out but nevertheless recurrence has taken place. The operations in this group have been performed by competent surgeons during the past twelve years. As a rule, subsequent to the return of these veins, multiple local injections have been given, and the existing vein pattern becomes definitely bizarre.

As the result of a study of thirty-two cases belonging to the second category where reoperation has been carried out, certain reasons for recurrence can be cited. It is difficult to be specific in all cases as to the exact cause of the recurrences, and therefore the subsequent list contains only those in which the causative factor was relatively definite.

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1. Despite an adequately high position of the groin incision, it was obvious in four cases that the saphenous ligation was made one inch or more distal to the saphenofemoral junction. The tributary veins remaining attached to the saphenous stump showed marked dilatation, and presumably allowed reconnection with this stump and the distal saphenous vein. This type of recurrence can be surmised from inspection of the groin area. Multiple new subcutaneous veins can be seen which the patient states have arisen since the operation.

2. On re-exploration of the saphenofemoral area, it becomes obvious that the initial surgeon has ligated only one limb of a high division of the saphenous vein into the relatively common inverted-Y anomaly. The other limb of the Y remains patent. This cause was found in three cases. The patient usually states that some early benefit followed this operation but that, after a period of months, the veins were about as obvious as before the operation.

3. Failure of the surgeon to identify and ligate an accessory saphenous vein is another cause. This abnormal branch, present in only 2 to 3 per cent of individuals and seen in this series on three occasions, usually joins the great saphenous vein at its concavity just before its entrance into the common femoral vein. However, in one instance it was found to join the common femoral vein one inch above the normal saphenofemoral junction. A proper dissection of this junction and exposure of the common femoral vein at the initial operation will prevent this oversight as well as those mentioned in Types 1 and 2.

4. Two cases were encountered in which the area of scarring about the saphenofemoral junction and the lack of the usual tributaries indicated that the surgeon had performed a proper ligation. A segment of vein had not been resected, and patency of the saphenous vein had again appeared. Catgut sutures had been used, and it is likely that this reopening was the result of absorption of the catgut ligature. Such a phenomenon is usual when a major artery has been ligated in continuity, and consequently it is entirely a possibility here, where pressures up to 400 mm. of water can be produced when the patient strains.

5. An incompetent small saphenous vein is too frequently missed in the initial assessment of the patient. It should be remembered that in 15 to 20 per cent of patients with primary varicose veins, this vein is involved either solely or in conjunction with great saphenous incompetence. Failure to ligate and remove this vein allows for continuing varices in the calf and lateral ankle region and a so-called recurrence.

6. The great majority of recurrences, twenty in this series, are the result of the missing, or the subsequent opening, of incompetent communicating veins between the saphenous systems and the deep venous circulation. The incompetent communicating veins result in recanalization of the original thrombosis, or dilatation and the production of varicosities in hitherto small superficial collateral channels. Attempts to locate accurately such incompetent communicators by the comparative or multiple tourniquet tests have,

in my hands, been far from successful. The majority connect relatively directly with the two saphenous systems, but others appear independently. It is the existence of this latter type which makes it impossible to promise cure in any case of primary varicose veins despite every known type of treatment.

In this catalogue of the causes of recurrent varicose veins, it is taken for granted that the varices associated with a previous deep phlebitis, congenital or acquired arteriovenous fistula, and cirrhosis of the liver have been ruled out. I have not found the type described as arterial varices except in conjunction with a localized or generalized congenital arteriovenous fistula.

TREATMENT

Further attention to these recurrent varicose veins is demanded by the patient for several reasons. The appearance of these deforming veins may be a primary factor, there may have been recurrence of eczema or ulceration, or the return of the symptoms originally experienced may bring the patient for further therapy.

The decision as to whether this further treatment should be conservative or radical depends, as originally, on whether a positive Trendelenburg test can be demonstrated. When this test is negative or doubtful for reverse flow on standing, then local injections of sclerosing fluid are all that is indicated. When it is obvious that the original valvular incompetence has recurred or persisted, local injections are merely temporary in benefit, and further surgery is indicated.

This secondary surgery should consist of a re-exploration of the saphenofemoral junction to correct the possible faults in this area and a stripping of the existing principal superficial veins. Prior to operation, the small saphenous vein should be carefully inspected in the popliteal area. When dilated, this vein can be palpated when the patient is erect. When doubt exists as to its state of incompetency, exploration of this area is indicated. Re-exploration of the saphenofemoral junction can be a most difficult procedure. Scar obliterates the landmarks and especially the areolar tissue which ensheaths the veins, making the dissection next to impossible. The recurrent veins in the scar are thin-walled, friable, and tortuous. Resulting troublesome bleeding harasses the surgeon. The following technique is offered to facilitate this religation and to ensure a proper high ligation of the saphenous vein.

The previous incision is reopened if it is placed in the fold of the groin. If the original scar is lower in the thigh, a new incision in the fold is made.

Following division of the scarred subcutaneous fat, the dissection is carried centrally, beneath the upper skin flaps, through normal fatty tissue toward the inguinal ligament. The common femoral vein is sought just distal to this ligament, and its position can be quickly determined lying medial to the readily palpable femoral artery. During this phase of the operation and during the subsequent stripping, the Trendelenburg position will be of assistance by reducing venous pressures. The femoral sheath is opened and the anterior half of the common femoral vein exposed. The usual surrounding areolar tissue about this vein has been undisturbed by the original operation and permits

easy dissection downward of the femoral vein to the saphenofemoral junction. If a proper high ligation had been made previously, scarring is again encountered at the fossa ovalis but, by keeping close to the sides of the femoral vein in this areolar envelope, the exposure can be carried below this junction. The common femoral vein is now exposed both above and below the saphenous junction, and it is a simple matter to pass a silk ligature about the saphenous vein for a proper flush ligation. This exposure also allows for detection of any accessory saphenous veins which join the main veins in this area. The saphenous tributaries can be disregarded once a proper proximal ligation has been carried out.

The remainder of the surgical procedure consists in isolating the great saphenous vein at the knee level or any other level where it can be seen or palpated with passage of an appropriate stripper toward the groin. In most cases it will be found to halt just distal to the previous scar, and the head of the stripper can be isolated by dissection through the lower part of the groin incision. Stripping of the vein downward from the medial knee incision is next carried out, and as large a segment of vein as possible is removed through another small incision. The lower end of the great saphenous vein is isolated just distal and anterior to the medial malleolus, and the stripper is passed upward as far as possible. It frequently follows an entirely different venous channel than that discovered at the medial knee and emphasizes the finding that reduplication of the great saphenous vein is not uncommon.

Stripping of a vein segment which has recanalized following a previous thrombosis from sclerosing fluids is not as easy as stripping a virgin vein. Perivenous thrombosis causes tethering, and considerable pull on the stripper is necessary. The vein may come out in fragments, and the job is not as clean-cut as in an uncomplicated case. The surgeon should not hesitate to excise segments which cannot be removed by the stripper. As mentioned previously, the saphenous tributaries are usually numerous and bizarre in these cases, and several postoperative visits are necessary as a rule to clear up these branches by local injections.

Thirty-two patients of Category 2 type of recurrent varicose veins have been reoperated upon in the past three years by this method. Twenty-four have been treated over one year ago and have reported, to date, complete to partial satisfaction with the result. Postoperative injections which were required ranged in all cases from a minimum of two to a maximum of eleven. With a follow-up of three years at the longest, it is difficult to be dogmatic about the eventual results. Undoubtedly more varices will appear in some of these patients, but it is likely that they can be held in check by the occasional injection given at the yearly visits which these patients are requested to make. Four of the thirty-two patients have required further injections to date, but the veins were small and readily responded to sclerosing therapy.

CONCLUSIONS

1. The causes of major recurrence in thirty-two patients with primary varicose veins previously operated upon who underwent further surgery are

discussed. Persistent or new incompetent communicating veins are the greatest single cause.

2. A new technique is described for religation of the saphenous vein at the femoral junction which obviates the difficulties and dangers of secondary surgery in this area.

3. The importance of the small saphenous vein as a cause of recurrence is stressed.

4. The results of a three-year follow-up have been satisfactory in the great majority, but the need for yearly visits and possible further local sclerosing injections is indicated.

THE USE OF INTRAVENOUS TRYPSIN IN EXPERIMENTAL PULMONARY EMBOLISM

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TRYPSIN is an enzyme which is known to hydrolyze (digest) certain proteins including fibrin and fibrinogen.[1] There occurs normally in the circulating blood of animals and man a small quantity of a proteolytic enzyme, fibrinolysin (plasmin),[2] which will also hydrolyze fibrin and fibrinogen. The precursor to fibrinolysin, profibrinolysin (plasminogen), also occurs normally in the circulating blood and in much larger amounts. There are many drugs, conditions, and disease states which will activate profibrinolysin to fibrinolysin[2-4] and increase the fibrinolytic activity of the blood. The amount of activation exhibits a species variation for some of the activators studied.[5-7] Streptokinase will activate this precursor a barely perceptible amount in sera of dogs[8] and a larger amount in sera of man.

In the search for a thrombolytic agent, enzymes known to hydrolyze fibrin have been studied. Johnson and Tillett[9] made use of the fibrinolytic enzyme occurring in the circulating blood. They administered streptokinase to rabbits intravenously. This enzyme activated the profibrinolysin to fibrinolysin and caused a gross increase in the fibrinolytic activity of the blood. They reported the complete lysis of clots in ear veins of rabbits twenty-three out of twenty-five times, resulting from the increased lytic activity. Innerfield and associates[10, 11] gave trypsin intravenously to dogs and rabbits after producing intravascular clots, and they reported the complete lysis of clots in some cases. They also reported the lysis of thrombi in patients with acute and chronic thrombophlebitis.

We[12] found that the administration of 130,000 U. of trypsin per kilogram intravenously in dogs would not cause lysis of an experimentally produced thrombus. Also, we found that the administration of 3,000 U. of trypsin per kilogram in human beings had no apparent effect upon the thrombi. However, our in vitro experiments[13] showed that if trypsin was added to blood before it was clotted, a small amount was required to lyse this clot as compared to the amount required to lyse a clot containing no trypsin.

The present experiments were conducted to determine whether intravenous trypsin administered prior to the production of experimental pulmonary emboli and again afterward would cause lysis of the emboli. A standard technique of production of pulmonary emboli was first established. Trypsin was administered intravenously after production of experimental pulmonary emboli in one series of dogs. In another series of dogs, trypsin was administered intravenously before, and again after, production of experimental pulmonary emboli.

Read at the seventh annual meeting of the Society for Vascular Surgery, New York, N. Y., May 31, 1953.

METHODS

Fifty-two healthy adult mongrel dogs weighing from seven to fifteen kilograms were used. A modification of the method of Holden and co-workers[14] was used. The external jugular veins were exposed on both sides for a distance of 8 to 10 cm. A rubber-shod bulldog clamp was applied to the proximal end of the exposed segment. The vein was gently milked toward the clamp to overcome spasm in the vein and to distend the vein with blood. A total of 500 U. of thrombin* (0.5 c.c.) was injected through a 27 gauge needle using three different sites along the vein. Bleeding from the puncture site was prevented by slowly injecting while the needle was being withdrawn from the vein. The vein segment was then massaged gently four or five times to insure mixing of the thrombin and blood. An immediate clot was formed and could be palpated and fractured between the index finger and thumb. Time from production of clots until their release into the circulation varied from five to forty-five minutes. The surviving dogs were sacrificed forty-eight hours later. The heart and lungs were quickly removed and examined immediately. The right ventricle was opened and inspected for emboli and mural thrombi, recent or old, and any recent extension of clots. The pulmonary arterial tree was carefully dissected and inspected for emboli. Specimens were taken from areas containing emboli for microscopic study.

Using this basic technique, certain variations were employed on twenty-six animals comprising the control group. In eight dogs the clot was produced in only one jugular vein. In six of these dogs the clots were released into the circulation forty minutes after formation and in one dog, five minutes after formation. The eighth dog received an injection of thrombin into one jugular vein without clamping off the segment. In eighteen other dogs the clots were produced in both jugular veins. The bilateral clots were released almost simultaneously into the circulation twenty minutes after formation in six dogs, and forty-five minutes after formation in eight dogs. In one dog, one clot was released after ten minutes. In three dogs the bulldog clamps were replaced with partially constricting ligatures ten minutes after clot formation.

Twenty-six dogs were treated with intravenous trypsin† at various times before and after clots were produced in both jugular veins. The thrombi were released into the circulation as in the control animals.

RESULTS

Control Series.—In the first six untreated animals with clots produced in only one jugular vein and released after forty minutes, the only effect was a slight increase in respiratory rate and depth shortly afterward, returning to normal after ten minutes. These animals were sacrificed after forty-eight hours. Post-mortem examination revealed pulmonary emboli in three of the six dogs.

*Thrombin, Topical (bovine origin), Parke, Davis & Company, 1,000 U vial.

†Enzar, developed, manufactured, and supplied by the Armour Laboratories, Chicago, consists of 90 per cent pure trypsin, 5 per cent ash (mostly magnesium), 4 per cent traces of ribonuclease plus cathepsin and alpha, beta, and gamma chymotrypsin, 1 per cent undetermined.

If the clot from one external jugular vein was released into the circulation five minutes after formation, death occurred in ten minutes. In one such experiment the right ventricle was found to contain a large, soft recent clot attached to an older clot cast in the shape of the jugular vein. In another animal, .025 c.c. (250 U.) of thrombin was injected into the unclamped external jugular vein. This also resulted in death in ten minutes and post-mortem findings of a large, soft clot in the right ventricle.

In the eighteen untreated animals with clots in both jugular veins, the results were as follows. Release of one or both jugular vein clots into the circulation ten minutes after formation resulted in death of each of four dogs within ten minutes after release. This was true even when partial occlusion was substituted for the bulldog clamps ten minutes after clot formation. All these animals had soft clots in the right ventricle, with or without pulmonary embolism. Simultaneous release of the clots into the circulation twenty minutes after formation resulted in death in ten minutes in two of the six dogs. The right ventricle contained recent soft clots, and large emboli were found in the pulmonary arterial tree (Fig. 1). The four surviving dogs were sacrificed at forty-eight hours, and in each instance large emboli were found in the pulmonary arterial tree. In one of these dogs, a mural thrombus was present in the right ventricle.

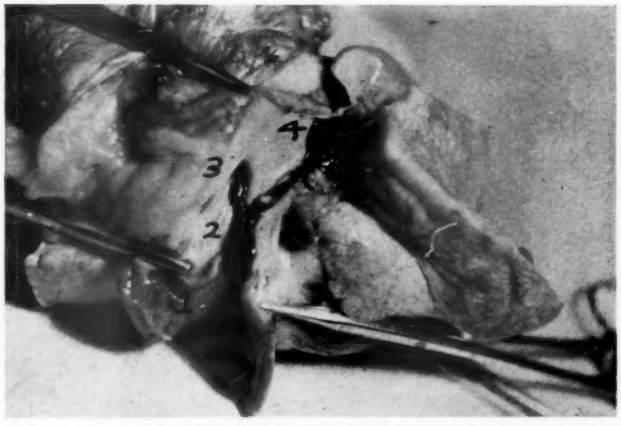


Fig. 1.—Fatal pulmonary embolism in control animal. The clots produced in the external jugular veins were released into the circulation twenty minutes after they were produced. The dog died ten minutes later. Large soft clot in right ventricle (*1*) extends into pulmonary trunk (*2*) and to ostia of right pulmonary artery (*3*) and left pulmonary artery (4), where it was attached to the emboli which almost occluded the ostia.

If the bilateral jugular vein clots were allowed to remain in place for forty-five minutes before release into the circulation, the animals survived, but at sacrifice forty-eight hours later they were found to have large emboli in the pulmonary arterial tree without intracardiac thrombi (Fig. 2). This result was consistent in eight dogs.

It was obvious from this series that jugular vein clots had to be produced bilaterally in order to result in the consistent formation of pulmonary emboli. Furthermore, release of the clots before they had an opportunity to inactivate

the thrombin resulted in death of the animals more from soft ventricular thrombi than from pulmonary embolism. Consistent production of firm pulmonary emboli in eight out of eight dogs was accomplished by releasing bilateral jugular vein thrombi into the circulation forty to forty-five minutes after formation. Death proved to be a poor criterion for the presence of pulmonary embolism in the dog. Only by sacrifice of the animal and dissection of the pulmonary arterial tree and heart chambers could the presence and extent of the embolizations be determined.

Fig. 2.—Standard pulmonary emboli in control animal. The dog was sacrificed forty-eight hours later. There is a large saddle embolus at branching of left pulmonary artery into arteries to the left upper and middle lobes (*1*) and extending into the right pulmonary artery (*2*). The emboli are firm and red, and have a nonshiny surface.

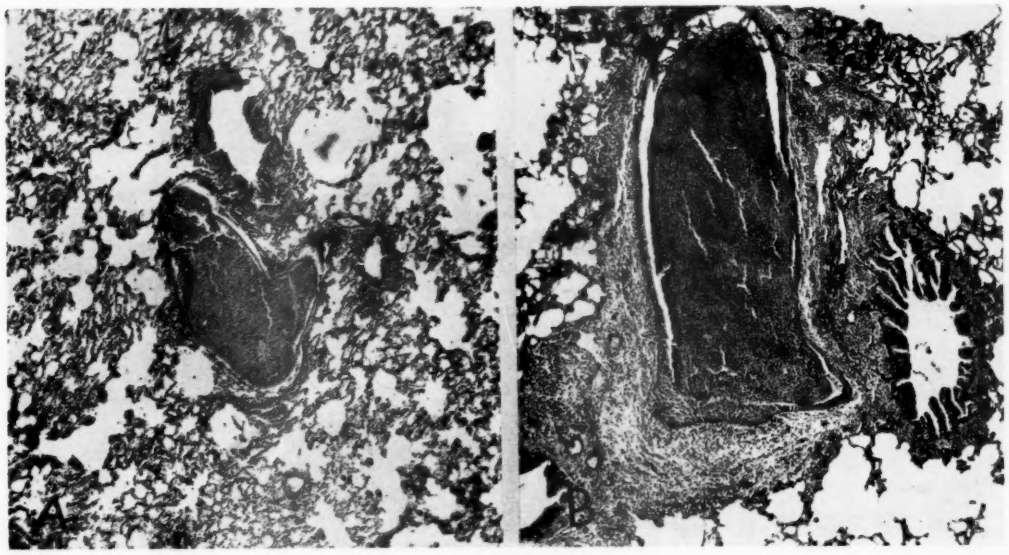
Series of Trypsin-Treated Animals.—Twenty-six dogs comprised this series. In five dogs, trypsin was given intravenously after pulmonary emboli were produced by releasing thrombi from both jugular veins. Trypsin was given in dosages varying from 25,000 to 120,000 U. per kilogram and in periods of time ranging from one minute to five hours. When as little as 25,000 U. per kilogram of trypsin was injected in one minute, death of the animal followed in from fifteen to forty-five minutes after injection. Two dogs died in shock, interpreted as peptone shock, resulting from the rapid injection of trypsin. In the remaining three animals, the trypsin was administered over a two- to four-hour period in the dosage of 120,000 U. per kilogram. One dog died in three hours and another dog in twenty-four hours; the third dog survived and was sacrificed at the end of forty-eight hours. Pulmonary emboli were found in all three of these animals (Fig. 3). Thus, the administration of trypsin, almost regardless of dosage, after a pulmonary embolism had been produced had no effect on the embolus.

Our next step was to administer trypsin before the clots were produced in both external jugular veins. In order to determine the size of trypsin dosage we performed certain in vitro experiments. We found that 100 U. of trypsin per cubic centimeter of oxalated blood would allow the blood to clot, but the clot would undergo subsequent lysis if kept at 37.5° C. in a water bath. Thus, assuming that the circulating blood volume of a dog was 12 per cent of its body

weight, a ten kilogram dog would have a total blood volume of 1,200 c.c. Therefore, the proper dosage would be roughly 12,000 U. of trypsin per kilogram as a preliminary administration of trypsin. To test this calculation, we injected 13,000 U. of trypsin per kilogram rapidly into dogs, and five minutes later a sample of blood was drawn. In each instance the blood clotted in the tube but the clot underwent lysis within twenty-four hours at water-bath temperature.

Employing this plan, six dogs were given 13,000 U. of trypsin per kilogram in 30 c.c. of saline solution intravenously in one minute. This resulted in an

Fig. 3.—Emboli in dog treated with trypsin after production of standard pulmonary embolism. Trypsin, 33,000 U. per kilogram, was given intravenously in five hours, and the animal was sacrificed forty-eight hours later. There is no gross evidence of digestion of the emboli. The emboli are black and have a shiny glistening surface.



A. *B.*

Fig. 4.—Photomicrographs of pulmonary emboli in control animal and in animal treated with trypsin.

A, Control section from lungs shown in Fig. 2; *B*, treated with trypsin after production of emboli. Section from lungs shown in Fig. 3. There is no microscopic evidence of digestion of the embolus in the trypsin-treated animal as compared to the control.

almost immediate drop in blood pressure to about 40 mm. Hg with return to control levels in about ten minutes. Bilateral jugular vein clots were then produced. In five dogs the clots were released into the circulation forty-five minutes later. Four of these dogs received an additional intravenous injection of 13,000 U. of trypsin per kilogram five minutes after release of the clots. Blood drawn five minutes after this injection did not clot, even after the addition of thrombin to the sample. The blood of these animals was now considered to be afibrinogenemic. This state lasted from two to four hours, after which there was gradual spontaneous restitution to normal clotting.

One of the four dogs so treated was found dead the morning after the experiment. Post-mortem examination revealed no clots in any of the pulmonary vessels or in the right ventricle. The other three dogs were sacrificed after forty-eight hours, and in none of these animals was there any evidence of pulmonary or ventricular emboli (Fig. 5). The fifth pretreated dog whose jugular vein clots were released forty-five minutes after formation did not receive the second injection of trypsin. It was found dead the following morning. Examination revealed no emboli in this animal, but the lungs showed a massive pneumonia with large amounts of mucus in the bronchi.

Fig. 5.—Dissection of the pulmonary arterial tree showing absence of pulmonary emboli.
A, Animal was given 13,000 U. of trypsin per kilogram intravenously in one minute. Pulmonary embolism was produced and an additional 13,000 U. of trypsin per kilogram was given. Animal was sacrificed forty-eight hours later.
B, Animal was given 19,000 U. of trypsin per kilogram in 175 c.c. of saline solution intravenously in one hour, ten minutes. Pulmonary embolism was produced, and an additional 16,000 U. of trypsin per kilogram in 125 c.c. of saline solution was given in fifty minutes. Animal was sacrified forty-eight hours later.

By error, the jugular vein clots in the sixth dog of this series were released just five minutes after formation. This dog died in ten minutes and was found to have a large, soft recent clot in the right ventricle and emboli in the pulmonary arteries (Dog 44, Table I).

In the next series of ten dogs, slower infusions of trypsin were given in an attempt to obviate the shock caused by rapid injection. We found that 19,000 U. of trypsin per kilogram in 175 c.c. of saline solution, infused over a period of one hour, ten minutes, usually resulted in the same degree of autolysis of a clot of drawn blood as did the one-minute injection of 13,000 U. per kilogram without lowering the blood pressure. Preinfusion and postinfusion circulating

fibrinogen levels were determined in some animals, and antitrypsin titers* were calculated. Seven of these dogs received only pretreatment, while three received an additional infusion of 16,000 U. of trypsin per kilogram in 125 c.c. of saline solution over a fifty-minute period after release of the jugular vein clots. Results in these animals are summarized in Table II. All animals survived and were sacrificed after forty-eight hours.

TABLE I. PRE-EMBOLISM DOSE OF 13,000 U. OF TRYPSIN PER KILOGRAM ADMINISTERED INTRAVENOUSLY IN 30 C.C. OF SALINE SOLUTION IN ONE MINUTE; POSTEMBOLISM DOSE THE SAME

DOG	AUTOLYSIS CLOT*	AFIBRINOGENEMIA	EMBOLI PRESENT
44	Complete	No	Yes; dog died ten minutes after clots released
45	Complete	After second injection	No
46	Complete	After second injection	No
47	Complete	After second injection	No; dead in cage next day
48	Complete	No; second injection not given	No; dead in cage next day

*Blood sample drawn, allowed to clot, and observed for autolysis after initial dose of trypsin.

TABLE II. PRE-EMBOLISM DOSE OF 19,000 U. OF TRYPSIN PER KILOGRAM IN 175 C.C. OF SALINE SOLUTION ADMINISTERED INTRAVENOUSLY IN SEVENTY MINUTES; NO ADDITIONAL TRYPSIN GIVEN

DOG	PLASMA FIBRINOGEN (MG. PER CENT)		TRYPSIN TITRATION OF PROTHROMBIN-PREE PLASMA (UNITS OF TRYPSIN)	AFIBRINOGENEMIA	AUTOLYSIS CLOT	EMBOLI PRESENT
	PRE-INFUSION	POST-INFUSION				
51	390	Not done	Not done	No	Complete	None
52	280	159	450	No	Complete	None
53	402	411	909	No	No	Present (see Fig. 6)
54	Not done	Not done	525	No	Complete	None
55	Not done	Not done	450	No	Complete	Small embolus
56	Not done	Not done	675	No	Complete	Small embolus
57	Not done	Not done	650	No	Complete	None

TABLE III. PRE-EMBOLISM DOSE OF 19,000 U. OF TRYPSIN PER KILOGRAM IN 175 C.C. OF SALINE SOLUTION ADMINISTERED INTRAVENOUSLY IN SEVENTY MINUTES. POSTEMBOLISM DOSE OF 16,000 U. OF TRYPSIN PER KILOGRAM IN 125 C.C. OF SALINE SOLUTION ADMINISTERED INTRAVENOUSLY IN FIFTY MINUTES

DOG	AUTOLYSIS CLOT	AFIBRINOGENEMIA	EMBOLI PRESENT
42	Complete	After second infusion	No
43	Complete	After second infusion	No
50	Complete	After second infusion	No

Four of the seven dogs with pretreatment alone had no evidence of cardiac or pulmonary embolism (Fig. 5, *B*). Two of the dogs were found to have small recent pulmonary emboli, and one had pulmonary emboli no different from those found in untreated animals. It is interesting that this dog (Fig. 6, No. 53

*Trypsin titration of prothrombin-free plasma determined the antitrypsin titer.[13] Prothrombin-free plasma was prepared by the method of Frommeyer and Epstein.[15] Varying small quantities of trypsin were added to 0.5 c.c. samples of prothrombin-free plasma. Thrombin was then added. The end point was taken as the concentration of trypsin in the tube in which a soft clot formed in one minute, provided the contents of the tube with the next higher concentration of trypsin remained liquid.

in Table II) had rather high fibrinogen levels, pre- and postinfusion, and an extremely high antitrypsin titer.

The three dogs in this group receiving an additional infusion of 16,000 U. of trypsin per kilogram after the release of the clots exhibited afibrinogenemia at the conclusion of this infusion. None of these animals had any evidence of pulmonary embolism when sacrificed forty-eight hours later (Table III).

Our subsequent experiments were concerned with variations in dosage of the trypsin before and after emboli were produced, with parallel determinations of pre- and postinfusion fibrinogen levels and antitrypsin titers, and observation of drawn blood for lysis of clots.

Fig. 6.—Dissection of the pulmonary arterial tree showing emboli present after treatment with trypsin. Animal was given 19,000 U. of trypsin per kilogram in 175 c.c. of saline solution in one hour, ten minutes. Pulmonary embolism was produced and no additional trypsin given. Animal was sacrificed forty-eight hours later.

Trypsin, 16,000 U. per kilogram in 175 c.c. of saline solution infused for one hour, ten minutes prior to formation of the jugular vein clots and 19,000 U. per kilogram after embolization, resulted in the absence of pulmonary emboli in one dog, but did not prevent the formation of two very small emboli in another dog. Blood drawn at the time of jugular vein clot production in the latter dog showed lysis of only two-thirds of the clot in the test tube in twenty-four hours. This indicated to us that the initial dose of trypsin by slow infusion was borderline to or below adequate levels, and therefore emboli could sometimes be expected almost regardless of the amount of the second dose. Fibrinogen levels and antitrypsin determinations were noncontributory in these animals (Table IV).

In two dogs the pre-embolism dose of trypsin was cut to 13,000 U. per kilogram, but the dose after release of the bilateral jugular vein thrombi was increased to 22,000 U. per kilogram. Both dosages were given by slow infusion. Clotted blood samples drawn after the first infusion did not completely lyse after twenty-four hours in the water bath. After the second infusion, a state of afibrinogenemia existed in each dog. Yet pulmonary emboli were found in each case, although they were not as large as those seen in control dogs. Antitrypsin levels were high in these dogs (Table V).

TABLE IV. PRE-EMBOLISM DOSE OF 16,000 U. OF TRYPSIN PER KILOGRAM IN 175 C.C. OF SALINE SOLUTION ADMINISTERED INTRAVENOUSLY IN SEVENTY MINUTES; POSTEMBOLISM DOSE OF 19,000 U. OF TRYPSIN PER KILOGRAM IN 125 C.C. OF SALINE SOLUTION IN FIFTY MINUTES

	PLASMA FIBRINOGEN (MILLIGRAMS PER CENT)					
DOG	PRE-INFUSION	AFTER FIRST INFUSION	TRYPSIN TITRATION OF PROTHROMBIN-FREE PLASMA (UNITS OF TRYPSIN)	AFIBRINOGENEMIA	AUTOLYSIS CLOT	EMBOLI PRESENT
61	397	327	750	After second infusion	Not complete	None
62	336	280	350	After second infusion	Not complete	Two small emboli

It would appear from these four experiments that the initial dosage of trypsin before embolization must be great enough to cause lysis of a sample of clotted blood drawn after the infusion in order to prevent the persistence of pulmonary emboli.

TABLE V. PRE-EMBOLISM DOSE OF 13,000 U. OF TRYPSIN PER KILOGRAM IN 175 C.C. OF SALINE SOLUTION ADMINISTERED INTRAVENOUSLY IN SEVENTY MINUTES; POSTEMBOLISM DOSE OF 22,000 U. OF TRYPSIN PER KILOGRAM IN 125 C.C. OF SALINE SOLUTION IN FIFTY MINUTES

	PLASMA FIBRINOGEN (MILLIGRAMS PER CENT)		TRYPSIN TITRATION OF PROTHROMBIN-FREE PLASMA		TRYPSIN TITRATION OF PLASMA				
DOG	PREIN-FUSION	AFTER FIRST IN-FUSION	PREIN-FUSION	AFTER FIRST IN-FUSION	PREIN-FUSION	AFTER FIRST IN-FUSION	AFIBRINOGENEMIA	AUTOLYSIS CLOT	EMBOLI PRESENT
63	468	412	400	350	600	400	No	No	Massive emboli; dog died after release of clots
64	468	280	1,000	350	1,250	750	After second infusion	No	Three small emboli
65	465	224	950	650	1,350	1,150	After second infusion	No	Two small emboli

One additional dog deserves special mention. This animal was given 13,000 U. of trypsin per kilogram as the pre-embolism dose. The animal was supposed to have received the 22,000 U. dosage after embolization, similar to the last two animals mentioned previously. However, the dog died ten minutes after release of the bilateral forty-five minute jugular vein thrombi and before the second trypsin infusion had been completed. Immediate post-mortem examination revealed large soft recent clots in both ventricles in addition to an older clot in the right ventricle shaped like the external jugular vein. The pulmonary arterial tree was completely cast with soft recent clotted blood containing several older clots (Dog 63, Table V). This unexpected finding might be explained on the basis of the persistence of some free thrombin around the embolus at the time of release or of an unusual amount of activation of prothrombin to thrombin by the trypsin.

SUMMARY AND DISCUSSION

In order for these experiments to be considered valid, it must be assumed that the method of producing pulmonary embolism in the control series of animals was valid. The size of our control series is small. Yet the fact that we found emboli in each instance by actual dissection of the sacrificed animals, rather than by the use of symptoms or survival as the criterion for the presence of pulmonary embolism, lends validity to the method. We found it necessary to produce clots in both external jugular veins in order to be assured of consistent pulmonary emboli. In order to allow survival for at least forty-eight hours, the jugular vein clots had to remain in place for forty-five minutes. If the clots were released into the circulation much sooner, there was apparently enough free thrombin in the embolized segment to cause rapid soft clot formation in the right ventricle and pulmonary arterial tree, and death. Evidence for this was seen in the animal in the control series in which thrombin was injected into the unclamped jugular vein. Death occurred in ten minutes, and a large soft clot was found in the right ventricle extending into the pulmonary artery.

Trypsin administered in almost any dosage after the production of pulmonary embolism had no effect on the emboli. This substantiates our previous work[12] which contradicted that of Innerfield and associates.[10, 11]

Infusions of trypsin before emboli were produced and again afterward usually prevented their persistence. Determination of dosage for the pretreatment infusion was based mainly on the observation of lysis of a clot of blood drawn five minutes after injection. A somewhat larger quantity of trypsin was necessary with slow infusion than with rapid injection to accomplish the same effect on the blood, which may be explained partially by the deterioration rate of trypsin solution. Rapid injections caused shock and were therefore undesirable.

At the time blood was drawn after the initial injection of trypsin, some delay in clotting was observed provided the dosage was adequate. Observation of drawn clotted blood for lysis revealed different rates of lysis occurring in the samples from various dogs given the same dosage by weight. Possible explanations for this finding include the variants involved in administering a drug on a weight basis, and perhaps differences in antitrypsin levels. As a rule, optimum infusion dosages caused the first postinfusion blood sample clot to undergo lysis over a period of eight to ten hours at 37.5° C. If more trypsin was infused, lysis occurred as rapidly as ten minutes after the clot formed in the tube. Further administration resulted in blood which was incoagulable and afibrinogenemic. An intravascular clot, released into the circulation at a time when lysis is demonstrated in drawn clotted blood, will be lysed by an additional dosage of trypsin. We found that the pre-embolism dosage is more important than the second dosage of trypsin. In our dogs, at least 19,000 U. per kilogram infused slowly as a pre-embolism dosage, followed by a similar postembolism dosage, was necessary to prevent embolism. However, rapid injections of 13,000 U. per kilogram were just as effective, although they caused temporary shock.

COMMENT

Great caution must be exercised in any attempt to project our experimental work to possible application in the human being, for two main reasons which are: (1) there is known to be a species difference in the fibrinolytic effect of trypsin,[3] and (2) the afibrinogenemia occurring in our successful experiments after the second infusion of trypsin would be a most undesirable postoperative consequence in human surgery.

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THE EMPIRIC USE OF GASTRIC RESECTION IN THE TREATMENT OF UPPER GASTROINTESTINAL HEMORRHAGE

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IN RECENT years the problem of upper gastrointestinal hemorrhage has received much attention in both the medical and surgical literature. Whether authors are inclined toward the conservative nonoperative treatment or surgical intervention, the fact stands out that timely and adequate blood replacement has greatly reduced the mortality of either method of treatment. From many such reports the consensus would seem to be that there is a group of patients who require emergency surgery if they are to survive. The size and importance of the group of patients requiring emergency surgery for the control of upper gastrointestinal hemorrhage differ greatly from one article to the next. It is not the purpose of this paper to indicate how to select these patients but, rather, once the decision to operate has been reached, to advocate the empiric use of gastric resection.

When operating for gastrointestinal hemorrhage, there is general agreement that with a lesion palpable in the duodenum or stomach, gastric resection is the operation of choice. Simple ligation of the bleeding point, gastroenterostomy, and/or vagotomy are a poor compromise at best. However, there are always a few instances in which no lesion can be felt. If the liver and spleen are normal, with few exceptions authors advocate a wide gastrotomy to locate the bleeding point but frequently have been unable to find one. It is our contention that gastrotomy not only prolongs the operation in a poor-risk patient but also is frequently futile. This contention is based both on the experience previously reported in the literature and the cases here reported.

Opinions vary greatly as to the extent to which preoperative studies should be made to establish the etiology of the bleeding. Some feel that surgery should not be undertaken without good proof of peptic ulceration. Other authors feel that these patients are in no condition to undergo gastrointestinal x-ray examinations and that if surgery is delayed to obtain x-ray pictures the patient will be lost. Certainly, the patient requiring emergency surgery for the control of hemorrhage is not a good candidate for x-ray studies. Also, inconclusive x-ray pictures have all too frequently been reported when taken during active bleeding. Normal gastrointestinal x-ray pictures taken after the bleeding has stopped have been reported in as high as 25 per cent of the cases studied. Relatively little has been written to explain the normal stomach and duodenum found either by x-ray examination or at gastrotomy. The role of minute gastric erosions in this problem has been emphasized by Wangensteen,[7] Crohn,[2] Ives,[5] and recently by Cooper and Ferguson.[1] These lesions cannot be shown by x-ray picture. In the fresh

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specimen they cannot be palpated and usually can be seen only after fixation. When demonstrated after fixation the erosion is a clear-cut entity following the expected pattern of location of gastric ulcers and not possibly confused with hemorrhagic gastritis. It is a common experience to find that at operation the bleeding has ceased and that the stomach and duodenum are empty. This situation coupled with a gastric erosion always too small to be seen explains the failure of gastrotomy.

In 1884, in a widely quoted report, Dr. Gallard[3] gave a classic description of two patients who died of exsanguination despite cold white wine, ergot, and rum. At autopsy the gastric erosion was overlooked at first but later demonstrated after fixation. A third case would have been described but the "seance" closed. Since that time little attention has been given to superficial gastric erosions other than by the authors mentioned. Unfortunately, from those cases previously reported elsewhere and those cases to be reported here, no clear-cut clinical picture can be drawn which will point to the diagnosis of gastric erosion. Sudden, painless, catastrophic bleeding in a previously healthy patient is suggestive, but perhaps 20 per cent of peptic ulcers first manifest themselves by such a hemorrhage. Because the medical treatment of hemorrhage from a peptic ulcer or a superficial gastric erosion is the same, no importance can immediately be attached to the differential diagnosis. The matter of prime importance is that this diagnosis be in the mind of the surgeon after the decision to operate has been reached. There is insufficient recorded experience to compare the prognosis following surgery for these two conditions. Because the diagnosis of gastric erosion cannot be made with certainty, except at operation, there is no information concerning the prognosis or instance of recurrence following medical care. However, in each of the four articles mentioned, the discussion of this condition would seem to have been initiated by recurrent hemorrhage when a gastrotomy alone was done.

During a three-year period, eleven patients from one surgical service at St. Joseph's Mercy Hospital were operated upon because of uncontrolled gastrointestinal hemorrhage. A gastric ulcer was found in four cases, a duodenal ulcer in three cases, and no lesion was palpated in four cases. This is about the same proportion of cases as that reported in the series of Cooper and Ferguson. They reported eighteen patients operated upon as emergencies, in six of whom no lesion was palpated in the stomach or duodenum. They performed the gastric resection as a "blind gastric resection." Here it is preferred to consider this a gastric resection on an "empiric basis."

Brief case summaries of four patients in whom no lesion could be palpated follow.

CASE 1.—A 30-year-old, single woman, a shoe clerk, was attending a customer when she suddenly felt ill and vomited a large amount of clotted blood. This she attributed to the fact that the customer's small daughter had recently vomited liberally about the store. She herself had never had stomach trouble. She rested at home during that day but early next morning she passed large clots of blood by rectum and vomited blood once again. She was admitted to the hospital as an emergency. Blood pressure was 90/60, pulse 108, hemoglobin 7½ Gm., red blood count 2.01 million. In the next thirty hours she received

4,000 c.c. of blood, but the blood counts were essentially unchanged and the bleeding from the rectum continued. Emergency operation was advised and accepted. At operation the stomach and duodenum were empty and no lesions could be palpated. As the liver and spleen were normal, immediate gastric resection was undertaken. As the Von Petz clamp was being put in place, the stomach was seen to be filling up with blood. It was opened and a small artery was seen to be spurting on the lesser curvature just at the point where the Von Petz clamp was to be applied. Resection was completed and the patient made an uneventful recovery. She received a total of 7,000 c.c. of blood in thirty-six hours. She is alive and well three years later.

CASE 2.—A 68-year-old retired businessman was admitted to the medical service complaining of anorexia, weight loss, and tarry stools. X-ray pictures elsewhere had been reported as normal for the gastrointestinal tract. He admitted the abuse of alcohol for many years. On admission the liver and spleen were not palpably enlarged. The hemoglobin was 8.4 Gm., the red blood count was 3,000,000, and liver function studies were normal except for a lowered prothrombin time. X-ray pictures demonstrated a diverticulosis of the sigmoid colon and a diverticulum of the second portion of the duodenum. Esophagoscopy failed to demonstrate esophageal varices. During the ten days of hospitalization he received 5,500 c.c. of blood with unmaintained improvement. Tarry stools continued, but no vomiting.

The early morning of the eleventh hospital day he awakened his private nurse by having three large bloody bowel movements in bed. One thousand cubic centimeters of blood was given rapidly because of the marked drop in blood pressure and rise in pulse. There seemed little improvement with this, therefore an additional 2,000 c.c. of blood was given and surgical consultation obtained. As his condition was not improving, emergency surgery was advised and accepted. At operation the liver and spleen were normal, the stomach and duodenum were empty. No lesion could be palpated in either bowel or stomach. Gastric resection was performed immediately with an uneventful recovery. He received 4,500 c.c. of blood in this thirty-hour period. The patient is alive and well two years later. When the stomach was seen in the fresh state no lesion could be seen or palpated. However, after fixation two-minute gastric erosions were demonstrated on the lesser curvature. Considering this, the normal x-ray pictures are easily understood and it is doubted that gastrotomy would have demonstrated these lesions unless they could have been made to bleed.

CASE 3.—A 70-year-old farmer was admitted to the hospital for the Phenylbutizon therapy of a gouty arthritis. During the nine days of treatment he received 200 mg., four times a day. This produced a remarkable improvement in the arthritis and he was ready for discharge. On admission a secondary anemia had been noted which responded to a transfusion. During the afternoon of the tenth hospital day he passed large tarry stools and became very weak despite 1,500 c.c. of blood. During the subsequent night he received an additional 4,000 c.c. of blood and the next morning when seen in surgical consultation he appeared as well as his 7 Gm. of hemoglobin indicated. Emergency surgery was advised and accepted but before he could be taken to the operating room he had several large bloody stools and went into shock. Cut-downs were placed at each arm and 1,000 c.c. of blood was given quickly and he was taken to the operating room. At operation the liver and spleen were normal, the stomach and duodenum were empty, and no lesion could be palpated in the bowel, duodenum, or stomach. Gastric resection was performed immediately. Recovery seemed satisfactory but the patient died on the fourteenth postoperative day without preceding elevation of pulse, temperature, or respiration except during the last twelve hours of life. No autopsy was granted. Examination of the fresh specimen revealed no ulcer, but after fixation a small erosion was seen low on the lesser curvature of the stomach. This lesion not found by careful inspection of the stomach out of the body could never have been seen by gastrotomy unless bleeding had been started. Unsatisfactory side reactions have been reported in as many as 35 per cent of the patients

Fig. 1.

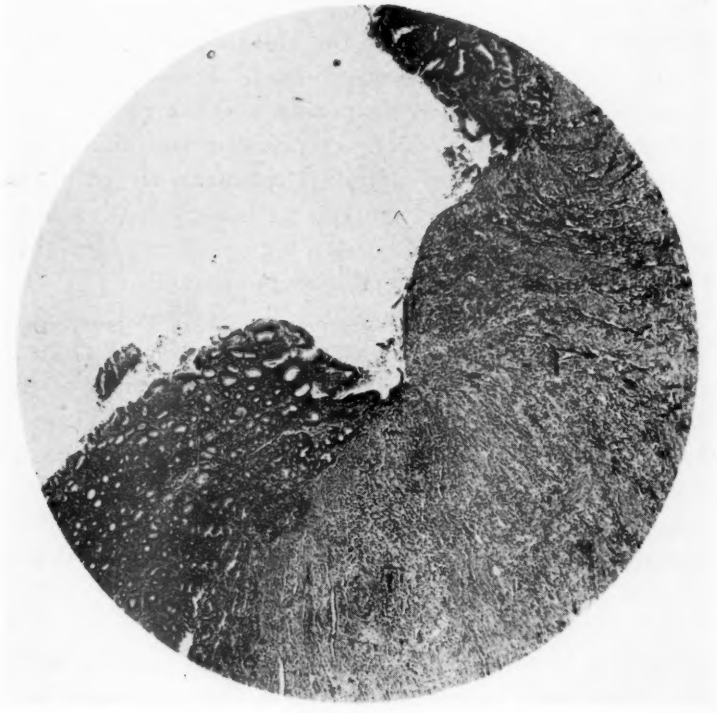

Fig. 2.

Fig. 1 (Case 3).—Photomicrograph showing gastric erosion following Phenylbutizon therapy. There is very little reaction in submucosa. Magnification 25 diopters, reduced one-third.)

Fig. 2.—Photomicrograph showing gastric erosion after eleven hospital days of bleeding. This has much the appearance of a miniature chronic gastric ulcer. (Magnification 25 diopters, reduced one-third.)

treated with Phenylbutizon.[4-6] These usually take the form of agranulocytosis or toxic reaction, but occasionally a duodenal ulcer has been activated or gastric hemorrhage has followed the use of Phenylbutizon.

CASE 4.—A 47-year-old professor was admitted as an emergency because he had suddenly vomited a large amount of blood. In 1935, a diagnosis of duodenal ulcer was first made for this patient, by x-ray examination. He was treated by diet and x-ray therapy. In 1944, he had a serious exacerbation, with a prolonged period of hemorrhage. In 1951, he had a minor exacerbation and at that time x-ray pictures showed some old scarring of the duodenum. Since then he has felt unusually well and has been very active. He had, however, had back pain the week prior to this illness and had taken an undisclosed amount of aspirin by mouth. On admission the patient soon passed several large bloody stools. During the next eighteen hours he received 3,500 c.c. of blood with a slow dropping in the hemoglobin and red blood count. He continued to have bloody stools by rectum, so emergency surgery was advised and accepted. Again at operation the liver and spleen were normal, and the stomach and duodenum were empty. No lesion could be felt in the stomach or duodenum but the gastric resection was performed without gastrotomy. The postoperative course was very satisfactory and he was discharged the ninth postoperative day. He received 5,500 c.c. of blood during a period of thirty-six hours. Again when the specimen was examined in the fresh state no lesion could be palpated or seen. However, after fixation a small superficial gastric erosion was demonstrated on the posterior aspect of the stomach. It was felt that a smaller erosion was seen higher up in the stomach but the microscopic examination failed to confirm this impression. There was no evidence of the so-called hemorrhagic gastritis that has been reported following the excessive use of aspirin.

The decision to operate on any of the eleven patients, and specifically in the four cases just detailed, may be questioned. It can only be stated that in each instance the situation seemed desperate and the prognosis poor without surgical intervention. However, once the decision to operate had been made the decision for gastric resection without demonstrating the bleeding point would seem to have been justified by the pathology that was demonstrated. Also, this decision would seem to be the logical answer to the situation in which no lesion is palpated in the stomach or duodenum.

There are two obvious weaknesses to this statement as presented here. First, in only one case was bleeding actually seen to come from a gastric erosion. However, in none of the other cases was there any evidence of hemorrhagic gastritis or other sources of hemorrhage seen by the pathologist. Second, no evidence has been given in this paper to show that gastrotomy alone is followed by recurrent hemorrhage. As previously mentioned recurrent hemorrhage has been reported in other series of cases and had drawn the attention of those authors to the existence of superficial gastric erosion.

SUMMARY

Once the decision to operate for uncontrolled gastrointestinal hemorrhage has been made, immediate gastric resection is the operation of choice if the liver and spleen are normal and a lesion is palpable in the stomach or duodenum. In those cases in which no lesion is palpated in the stomach or duodenum, gastric resection is advocated without gastrotomy to prove a bleeding point. Gastrotomy prolongs the operation in a poor-risk patient and frequently fails to show the bleeding point. Superficial gastric erosions, which

can neither be felt nor seen in the fresh specimen but which can be the source of exsanguination, are offered as the explanation of the hemorrhage when no lesion can be demonstrated by gastrotomy or later by x-ray picture. Four such cases are presented.

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MALIGNANT LESIONS OF THE THYROID

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INTRODUCTION

THE last decade has brought forth an increased interest in malignant diseases of the thyroid, partly because of the relative increased safety of radical head and neck surgery in the elderly, and particularly since radioactive materials have become available as an adjunct to diagnosis and therapy. Undoubtedly further strides will be made, and the present report concerns a review of the primary malignant lesions of the thyroid which were observed, treated, and followed at the University of Minnesota Hospitals over a twenty-eight year period, from June, 1924, to June, 1952. In order to give the figures significance, only those 101 cases in which the patients had histologically confirmed cancers were included in this study. The data were gathered from hospital files, tumor clinic follow-ups, x-ray therapy files, letters to local physicians, and reports from the Bureau of Vital Statistics.

It has long been recognized that one of the chief sources of difficulty in the management of thyroid lesions is the establishment of the clinical and, particularly, the pathologic diagnoses, of benignancy or malignancy. For this reason the incidence of malignancy in thyroid disease is not definitely known.[1] An average figure, derived from cumulative reports in the literature, has been quoted at about 3 per cent of all thyroid lesions. In 1946, 0.4 per cent of all cancer deaths were due to thyroid malignancy, a figure which equals that of cancer of the mouth. The average incidence in the state of Connecticut, from 1940 to 1946 was 1 per 100,000 population. There is recent increasing evidence that some thyroid cancers, particularly those that are less well differentiated, are in reality secondary lesions rather than primary thyroid malignancies.[1] The pathologist's responsibility is indeed a heavy one. Because many thyroid malignancies differentiate to such a high degree that the microscopic features closely simulate normal thyroid tissue, it is often extremely difficult to make a definitive diagnosis, particularly on frozen section. His responsibility is further weighted by the well-documented fact that any thyroid tumor which can be diagnosed clinically as being malignant is almost invariably beyond the stage of being resectable. It is the recognition of this fact that has served to increase the index of diagnostic suspicion. However, as a result of the increased surgical material presented to him in the past twenty years, the pathologist is now in a less vulnerable position except for a few lesions, particularly those classed as "metastasizing struma," which continue to be confusing.

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The statement is not infrequently made that patients with thyroid disease have a strong family history of some thyroid disorder. In this group of 101 cases there were 21 instances in which an immediate relative had had a goiter, and, in 6 of these 21, there was reason to suspect that the "goiter" was a cancer, in that the said relative subsequently died of cancer of the neck or throat.

Twelve patients of the entire group had had previous thyroid surgery. In 9 of these 12 the original material was available for review by our pathologists. In 6 cases the original diagnosis of a benign lesion was confirmed. In the remaining 3 the original diagnosis was reversed as having actually been malignant. In the 3 cases in which the original slides were not available, although the interval between the original surgery and the onset of the present lesion was quite long (mean of eleven years), one cannot say with certainty that the original lesion was benign, for a slow-growing papillary carcinoma can recur as long as twenty-five years postoperatively.[2]

Of the entire group of 101 patients, in 89 instances there was a clinical diagnosis or impression available from the chart. In only 52 instances (58 per cent) there was mention of a diagnosis or suspicion of malignancy; in the remaining 37 cases (42 per cent) the diagnosis was that of benign disease which at operation or on pathologic report was found to be malignant. It should also be pointed out that 36 cases had metastases either regional or distant when first seen. Actually, therefore, in only 16 cases (18 per cent) was the clinical diagnosis in any way astute! Further review of the charts showed 44 cases in which adequate clinical description was available for comparison with the gross operative or pathologic report. In 24 instances, or slightly more than one-half of this latter group, was there any reasonable correspondence of these descriptions. This strongly suggests that the attitude toward all thyroid swellings, clinically single, diffuse, or multiple, should assume the same index of suspicion which we now hold for swellings in the breast. Many studies have attempted to determine the incidence of malignancy in single nodules of the thyroid. Ward[3] found that 22 per cent of clinically solitary nodules were malignant. Others have found higher and lower incidences; Lahey[4] found 10.04 per cent of single nodules and 0.64 per cent of multiple nodules; Cole[5] reports 24.4 per cent of single nodules and 9.8 per cent of multiple nodules. The wide discrepancies between studies are interesting per se. Suffice it to say that such factors as the geographic region (goiter belt), variances in definitions, controversial pathologic diagnoses, etc., still do not completely resolve these discrepancies in the incidence of malignancy. For teaching purposes and as a general policy we have adopted the average figure of a 7 per cent incidence of malignancy in single nodules. This is the approximate incidence of malignancy of single clinically benign nodules in the breast and, therefore, the necessity of surgical excision can be emphasized. Actually the higher incidence of malignancy reported by some authors, even of multiple nodules, would suggest that this dictum of excision of thyroid nodules be extended to include all nodular goiters.

A factor which may partly explain the relatively large number of patients (36 of 101) who had metastases when first seen, was the long interval between the time the patient first noticed the goiter and treatment. In 86 patients this period was available from the medical history chart. It ranged from less than one month up to forty-five years, with a mean duration of sixty-eight months. This approximates Cole's[5] figure of seventy-three months. This long interval serves to reinforce the impression that most carcinomas of the thyroid arise in benign nodules or adenomas. In 12 of the 86 cases the patients had been under the observation of a physician for a period of years and had been given Lugol's solution or advised to do nothing despite suggestive symptoms of neoplasm.

The age of the patients is shown in Table I. It can be seen from this table that the majority (82 per cent) occurred in the older age groups, yet almost one patient in five was under the age of forty. The average age of this group was 55.5 years, which is a little older than that of other reported series.[5-7] It has been generally appreciated, however, that the average age for thyroid carcinoma is lower than that of most other malignancies because it is relatively common in adolescents.

TABLE I. AGE DISTRIBUTION

	AGE IN YEARS								
	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90
Number of cases	0	4	2	12	15	21	24	22	1

Sex.—The sex distribution (Table II) is in agreement with other reported series in being predominantly female. Seventy-three of the cases occurred in women, a ratio of approximately 3:1. Ward[3] has repeatedly stressed the comparatively high incidence of carcinoma in the male nontoxic multinodular goiter. Of this series of 101 patients, 29 had adenomatous goiters. Of these, 10 were men, indicating a slight definite preponderance in this group.

TABLE II. SEX DISTRIBUTION

SEX	NUMBER OF CASES	PER CENT
	101	100
Male	28	27.7
Female	73	72.3

TABLE III. PRESENTING COMPLAINT

Swelling in neck		57
Pressure		
Hoarseness		
Dysphagia		
		19
Dyspnea		
Cough or hemoptysis		
Weight loss		2
Pain		7
Weakness		3
Symptons of thyrotoxicosis		6
Not available		7
Total		101

Signs and Symptoms.—The presenting symptom, that is the outstanding complaint bringing the patient to his doctor, was available in 94 patients in the series. These are listed in Table III. As shown in the table the majority had a simple swelling of the neck and sought advice mainly because of the cosmetic deformity. Nineteen had pressure symptoms as a leading complaint. Six of the group presented with thyrotoxic symptoms; however, only 1 had a typical picture of Graves' disease. Pain was not a common complaint and when present was almost invariably the result of regional or distant metastases.

The over-all nature of the symptoms and signs, as obtained from physical examination of the patient, is shown in Table IV. Ninety-six of the entire group of 101 had a palpable lesion, and in almost one-half of the cases pressure symptoms were experienced. As noted, there is a relatively high incidence of thyrotoxicosis. These were judged on the basis of history and physical findings, basal metabolism rate (BMR) studies, and, in 2 patients, a significantly reduced serum cholesterol level. In only 1 of the 11 thyrotoxic patients was there reason to feel that the increased BMR was due to widespread metastases to bone and soft tissues. Crile[10] has suggested this occurrence as a plausible explanation for the variance in the incidence of thyrotoxicosis in reported series of thyroid malignancy. In 5 of these patients the BMR was over 40 on repeated determinations. As mentioned, one case was classically Graves' disease. In the literature, the highest incidence of thyrotoxicosis and malignancy is that of Pemberton and Lovelace, their figure being 33.5 per cent.[8, 9] McSwain and Diveley[11] quoted an incidence of 10 per cent in their series. However, in spite of these figures, the prevalent opinion is that one should make the diagnosis of malignancy with extreme caution in the presence of frank hyperthyroidism. There is general agreement that the carcinomatous tissue itself usually does not have a hyperthyroid function.

TABLE IV. TOTAL PHYSICAL SIGNS ON ADMISSION

Thyroid swelling	
Single	57
Nodular	29
Diffuse	10
Pressure	
Hoarseness, Dysphagia, Dyspnea, Cough	47
Weight loss	11
Pain	7
Weakness	3
Thyrotoxicosis	11
Metastases	
Regional	16
Distant	20
Not available	1

As indicated in Table IV, 36 patients presented with metastases; 16 were regional, and 20 were more widely disseminated. Included in the 16 regional cases are 5 cases of so-called "aberrant" thyroid carcinoma. Although the 20

patients with distant metastases were considered incurable, in a few instances the primary lesion was resectable and radon implantation carried out. This served to relieve pressure upon the trachea and was felt to be advisable in those cases which might be suitable for radioiodine therapy. In addition to these 36 cases, 23 patients developed metastases during their follow-up. Of these, 8 were regional (not uncommonly in the thyroid scar), and 15 were distantly disseminated. The distribution of all metastases is shown in Fig. 1.

This distribution parallels the experience of most investigators[8, 14] who have emphasized the predilection of thyroid metastases for lungs and bones.

Pathology.—Of the entire series, 3 patients were classified as having lymphoblastomas (1 Hodgkins, 2 lymphosarcomas), adenocarcinoma being diagnosed in the remainder. Of the latter, 5 were not classified because of their extremely uncharacteristic microscopic picture. The pathologic diagnoses are listed in Table V.

It should be emphasized that relatively few cases show a histologic picture which is uniform in type. If enough sections are reviewed from any one case, many features are seen which would justify a multiplicity of diagnostic terms. In the described classification, a given lesion was named according to the predominating structural form as described in the pathologic report. The real purpose of dividing any group of thyroid cancers in this way is the significantly different clinical prognosis of the various forms, and the necessity of planning the over-all therapy, whether by surgery, x-ray, hormones, radioactive iodine, or a combined approach, that will afford the best possible chance for cure to each patient. The recognized tendency of the more differentiated forms to take up radioactive iodine has been noted by many.[12]

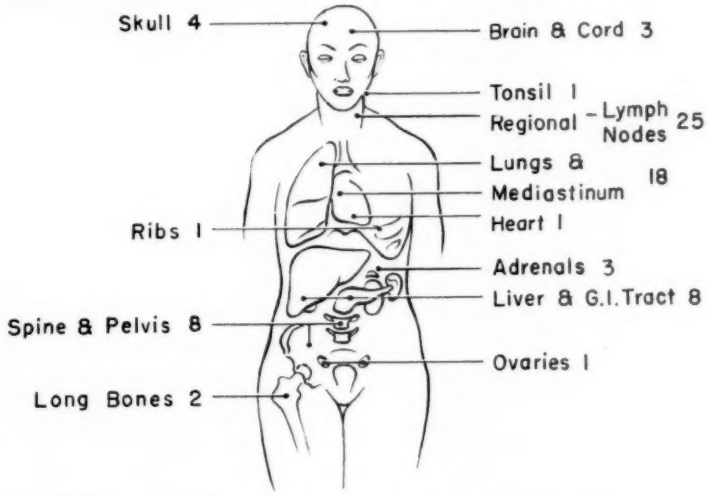

Fig. 1.—Distribution of metastasis-thyroid carcinoma.

Treatment.—In many instances the diagnosis of carcinoma was not made until the paraffin sections had been reviewed and, therefore, the primary treatment was based upon the clinical diagnosis and the appearance of the gland at the time of surgery. Where the clinical diagnosis of a widespread rapidly

growing lesion was obvious, nothing save a tracheotomy and biopsy could, as a rule, be carried out. Significant treatment data were available in 96 cases and are outlined in Table VI.

TABLE V. PATHOLOGIC CLASSIFICATION OF THYROID MALIGNANCIES

Metastasizing struma	2
Papillary	37
Follicular and alveolar	18
Solid adenocarcinoma	23
Hürthle cell	2
Spindle or giant cell	8
Anaplastic	3
Lymphoblastoma	3
Unclassified	5
Total	101

TABLE VI. TREATMENT OF MALIGNANT LESIONS OF THE THYROID

Number of cases		96
Metastases when first seen—regional or distant		36
Biopsy only (usually with radiation)		32
Patients submitted to surgery		64
Patients operated on for cure	44	
Patients operated on for palliation	20	

TABLE VII. SURGICAL PROCEDURE

PROCEDURE	NODULECTOMY	SUBTOTAL BILATERAL LOBECTOMY	TOTAL LOBECTOMY	TOTAL LOBECTOMY AND RADICAL NECK DISSECTION	TOTAL THYROIDECTOMY	TOTAL THYROIDECTOMY AND RADICAL NECK DISSECTION
For cure (44)	8	8	13	6	6	3
For palliation (20)	0	13	3	1	3	0

The type of surgical procedure carried out is listed in Table VII.

Of the entire group, 64 were submitted to a major surgical procedure. This represents an operability rate of 63.3 per cent. This is higher than many reported series which average about 50 per cent. Of these 64 cases, 46 received a full course of radiation therapy immediately or very soon after they recovered from the operative procedure. Eighteen patients were treated by surgery alone, either because they refused radiation therapy or did not survive long enough to obtain a full course of treatment. Almost all of the 37 patients who were treated nonoperatively received some radiation therapy. Thirty-two of these 37 had distant metastases or else the lesion was so locally invasive that resection was not feasible. Admittedly, most of the latter group were hopeless cases. Those patients who were treated surgically and listed as palliative were classified as such, mainly for two reasons. In some cases a subtotal thyroidectomy had been performed and malignancy was not discovered until the report on the paraffin section was returned. In others, although all gross tumor was removed, the lesion had invaded the tracheal cartilages or the muscular esophagus and had to be cut away by sharp dissection for removal of the primary tumor.

Isotope Therapy.—Twenty-six patients were given tracer doses of radioactive iodine (I^{131}). Of these, only 7 received a trial with a therapeutic dose. Among these 7 cases the highest uptake was 29 per cent, so it can be seen that, at best, the results could not be expected to be dramatic; moreover, many of these cases were far advanced and hopeless. The reports in the literature[12] state that 15 to 20 per cent of thyroid malignancies will take up significant amounts of radioiodine. This is consistent with our experience. Histologic grading of these lesions and their affinity for iodine expressed as measured uptake are shown in Table VIII. As might be expected, all but one of these tumors was well differentiated. Of several interesting cases 2 deserve further mention.

TABLE VIII. THERAPEUTIC RADIOIODINE THERAPY

PATIENT	PATHOLOGIC DIAGNOSIS	RADIOIODINE UPTAKE (PER CENT)	RESPONSE
E. B.	Papillary adenocarcinoma	22.0	Satisfactory
M. F.	Spindle cell adenocarcinoma	4.6	Poor
A. H.	Follicular adenocarcinoma	29.0	Poor*
J. M.	Papillary adenocarcinoma	22.0	Good
M. M.	Metastasizing struma	22.0	Satisfactory
S. W.	Alveolar adenocarcinoma	19.0	Satisfactory
C. C.	Follicular adenocarcinoma	9.8	Satisfactory

*Died of concomitant cancer of breast with metastases.

CASE 1 (O. C., University Hospitals, No. 799726).—This 43-year-old farmer was referred to the University Hospitals for treatment in February, 1949. Since the age of 18 years, he had noticed a continuously enlarging nodule in the neck which caused no symptoms and was described by his doctor as being a goiter. Between 1938 and 1940 he was treated by daily medication with iodine and pills. In 1946 the mass had involved the entire right side of the neck and interfered with his ability to sleep on the right side. In December, 1946, his local physician performed a subtotal thyroidectomy, removing in addition a nodule from behind the right ear which was diagnosed as metastatic thyroid carcinoma. He was given twenty-three x-ray treatments over the entire right cervical area. Six months later, two other lumps appeared on the right side of the neck, one in front of the ear and one over the collar bone. In March, 1948, excision of these lumps was attempted under local anesthesia by his physician, and the biopsy reports were again reported as metastatic thyroid carcinoma. These nodules did not disappear entirely after surgery, and in October, 1948, the patient was referred to the University Hospitals for further treatment. Review of his slides showed a follicular adenocarcinoma. On Oct. 19, 1948, a tracer dose of radioactive iodine was given orally, and approximately 21 per cent uptake was retained by the normal thyroid. The metastatic masses also took up an appreciable amount of iodine (9.8 per cent). For this reason it was decided to thyroidectomize the patient with large doses of radioactive iodine. This was accomplished with 20 mc. of I^{131} administered a few days later. One month later the patient complained of a feeling of tiredness, weakness, slight weight increase, loss of appetite, and susceptibility to temperature changes.

On Dec. 17, 1948, the patient was admitted to the hospital and 23 mc. of I^{131} was given orally. A second dose of 77 mc. was administered on Jan. 3, 1949. The symptoms of myxedema became worse and he was placed on 3 gr. of thyroid a day. The large metastatic masses, which were previously considered inoperable by reason of their fixation and extension through the deep tissues below the attachment of the sternomastoid to the mastoid, and the posterior surface of the clavicle, were now found to have decreased markedly in size.

On March 4, 1949, the patient was taken to surgery with a view to resecting the residual tumor masses. Surgical excision* included the medial two-thirds of the clavicle, a radical

*Performed by Dr. R. L. Varco and Dr. G. E. Moore.

neck dissection, removal of the sternomastoid muscle from its origin at the mastoid with ligation of the internal jugular vein at the base of the skull. The dissection was made difficult by much capillary oozing, likely the result of the previous irradiation, both deep x-ray therapy and the radioiodine.

The pathologic report stated that both tumor masses consisted of metastatic carcinoma of the thyroid, the acini containing colloid material, while others showed papillary projections with lesser amounts of colloid. Mitotic figures were scarce. Subsequent examination of the patient in September, 1949, revealed no recurrence of tumor. At present the patient is engaged in farm work and, except for some disability as a result of the removal of his clavicle, has had no recurrence. He requires 3 gr. of thyroid daily.

It is too early to predict the final outcome in Case 1, yet the palliation afforded by a combination of isotope therapy and surgical excision of residual tumor is encouraging. Certainly at the time surgery was contemplated on the patient's original visit to the hospital, the size and fixation of the metastatic masses were such as to discourage the most aggressive surgeon.

CASE 2 (M. M., University Hospitals, No. 817908).—This 62-year-old man first noticed a solitary lump in the left thyroid region in 1943. It enlarged very slowly until 1947, when his local physician advised a thyroidectomy. An enucleation of the nodule was carried out and the pathologic report read as a "benign colloid adenoma."

The patient remained well until July, 1949, when he noted the onset of pain and swelling in the left axillary region. X-ray examination revealed an expanding lesion of the left sixth rib in the anterior axillary area. This was biopsied and reported as adult thyroid tissue, the diagnosis being that of "benign metastasizing struma." He was subsequently referred to the University Hospitals for further treatment. When seen here in May, 1950, he had a small nodule in the lower pole of the left lobe of the thyroid and a healed biopsy incision over a 4 cm. mass in the left sixth rib at the axilla. A bone survey was negative except for the destructive lesion in the left sixth rib. A tracer dose of radioiodine revealed a normal (22.2 per cent) uptake in the thyroid area, but none over the rib lesion.

On May 11, 1950, a total thyroidectomy was carried out. Pathologic examination showed both lobes to contain numerous small circumscribed adenomas which were histologically benign, and identical with the original adenoma removed in 1947. The diagnosis was that of multiple well-differentiated malignant adenomas.

A tracer study carried out on June 15, 1950, revealed no uptake over the rib lesion and a 4 per cent uptake in the thyroid area. A relative protein-bound iodine determination (seventy-two hours) was 65 to 70 per cent. This was interpreted as indicating the presence of functioning thyroid, likely in the form of the metastases. At this time, planographic studies of the chest showed a second destructive lesion in the body of the manubrium. Because pain was becoming a prominent symptom, it was decided to admit him and excise the rib and sternal metastases. On Aug. 1, 1950, a second tracer study was carried out, and at this time the uptake over the manubrium and rib lesion was 7 per cent, indicating that functioning thyroid tissue was now present. It was therefore decided to give him a therapeutic trial of radioiodine; 100 mc. was administered in two doses over a five-day period. He was also treated with external radiation following his discharge from the hospital, receiving a total of 4,200 roentgens in air over the manubrium. In November, 1950, the rib lesion was noted to be smaller, but the manubrial metastasis remained unchanged. A tracer uptake revealed the presence of active tissue in the neck, manubrium, and sixth left rib. At this time it was elected to employ a preliminary dose of thyroid-stimulating hormone and then to administer a further therapeutic dose of I^{131} as well as external radiation therapy. Follow-up study showed a slight decrease in the size of the metastases.

In February, 1951, the patient returned with recurrence of pain in the region of the left sixth rib, and it was elected to excise the rib lesion and intercostal bundle. This was done on Feb. 23, 1951, and pathologic examination disclosed a well-differentiated colloid containing metastasis. The postoperative course was uneventful. The patient was placed on desiccated thyroid and discharged.

Frequent follow-ups in the Tumor Clinic showed that the patient gained weight and felt well except for a mild cough. When he was last seen it was felt that no further therapy was necessary.

Case 2 is cited to stress the peculiar biologic nature of many thyroid cancers. The problems facing the pathologist, as well as the complexities involved in employing radioiodine, cannot be overemphasized.

Morbidity and Mortality.—

Morbidity:

A. Surgical (8 cases): There were 7 cases of recurrent laryngeal nerve injury which occurred at surgery and persisted after the

TABLE IX. SURGICAL MORTALITY

CAUSE	NUMBER OF CASES	TIME OF OCCURRENCE
Tracheal collapse	1	Fourth postoperative day
Tracheal obstruction	3	Second to tenth postoperative day
Common carotid ligation	1	At operation
Coronary insufficiency	1	Third postoperative day
Pneumonia	1	Sixth postoperative day

TABLE X. OVER-ALL SURVIVAL FOR THYROID CARCINOMA

YEAR	NUMBER OF CASES	SURVIVAL (YEARS)																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1924	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
1925	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1926	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0
1927	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1928	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1929	2	2	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
1930	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1931	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
1932	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1933	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1934	4	3	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1935	4	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	
1936	7	4	4	4	4	4	4	4	4	4	4	3	3	3	3	3	3		
1937	7	3	3	3	3	2	2	1	1	1	1	1	0	0	0	0			
1938	3	2	2	2	2	2	2	2	2	2	1	1	1	1	1				
1939	2	2	2	2	2	2	2	2	2	2	2	2	2	1					
1940	3	1	1	1	1	1	1	1	1	1	1	0	0						
1941	6	4	4	4	4	3	3	3	3	1	1	1							
1942	7	3	3	2	1	1	1	0	0	0	0								
1943	2	1	1	1	1	0	0	0	0	0									
1944	3	2	2	2	2	2	2	2	0										
1945	7	3	3	1	1	1	1	1											
1946	5	5	3	3	3	3	3												
1947	4	2	2	1	1	1													
1948	11	8	8	6	2														
1949	4	2	2	2															
1950	3	1	1																
1951	6	5																	
1952	1	1																	
Cases	98	98	97	91	88	84	73	69	64	57	54	52	45	39	36	34	31	24	17
Survivals		62	53	43	34	29	26	20	17	15	13	11	9	8	6	5	5	2	1
Per cent survivals		63	54	47	38	34	35	29	26	26	24	21	20	20	16	14	16	8	6
Corrected per cent survival		63	54	48	40	37	37	30	28	29	26	23	20	23	19	17	19	12	11

operation. One of these was bilateral. The other surgical complication was a severe wound hematoma.

B. X-ray: There were 4 cases of severe x-ray dermatitis. Three of these were followed by extensive scarring.

Mortality: Seven patients died of causes consequent to a surgical procedure. These are listed in Table IX.

As 64 patients were treated surgically this results in an operative mortality of 10 per cent. Portmann noted a mortality of 8.5 per cent. Such figures are a reflection of the increased technical difficulties of dealing with a malignancy in the thyroid area, of the use of more radical procedures, as well as of the advanced age of many of these patients. As has been stressed repeatedly, this should be considered one of the strongest arguments for prophylactic removal of all thyroid nodules at a time when this is easily accomplished and when the mortality and morbidity are each well under 1 per cent.[4]

Results.—The over-all survival rate for 98 patients of the entire group of 101 is shown in Table X. Three cases of lymphoblastomas are not included. In addition 4 patients who were lost to follow-up are presumed dead of their disease. In terms of percentage, the three-, five-, ten-, and fifteen-year survivals are 47 per cent, 34 per cent, 24 per cent, and 14 per cent, respectively. Five

TABLE XI. OVER-ALL SURVIVAL OF CASES TREATED WITH SURGERY*

YEAR	NUMBER OF CASES	SURVIVAL (YEARS)																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1924	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
1925	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1926	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1927	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1928	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1929	2	2	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
1930	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1931	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
1932	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1933	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1934	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1935	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	0
1936	4	3	3	3	3	3	3	3	3	3	3	2	2	2	2	2	2	0	
1937	5	3	3	3	3	2	2	1	1	1	1	1	0	0	0	0	0		
1938	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			
1939	2	2	2	2	2	2	2	2	2	2	2	2	2	1	0				
1940	2	1	1	1	1	1	1	1	1	0	0	0	0	0					
1941	3	3	3	3	3	2	2	2	2	0	0	0	0						
1942	1	1	1	1	0	0	0	0	0	0	0	0							
1943	1	1	1	1	1	0	0	0	0	0	0								
1944	2	2	2	2	2	2	2	2	2	0									
1945	5	3	3	1	1	1	1	1	0										
1946	5	4	3	3	3	3	3	0											
1947	4	2	2	1	1	1	0												
1948	7	7	7	6	2	0													
1949	3	2	2	2	0														
1950	2	1	1	0															
1951	6	3	0																
1952	1	0																	
Cases	64	64	63	57	55	52	45	41	36	31	29	28	27	24	22	20	19	14	10
Survivals		48	44	35	29	24	21	16	15	10	9	8	7	6	5	5	4	2	1
% Survival		75	70	61	52	46	46	39	41	32	31	29	29	25	23	25	28	14	10

*Forty-six had additional radiation.

patients who died of unrelated causes and were apparently free of disease at the time are included in these figures. If we correct for this latter group, the survival rates are slightly higher, 48 per cent, 37 per cent, 26 per cent, and 17 per cent, respectively.

Of the 64 cases treated surgically, the results are shown in Table XI. Forty-six of this number received a full course of radiation therapy. In the remaining 18, x-ray treatment was not given, was incomplete, or else the patient succumbed after the surgical procedure. The three-, five-, ten-, and fifteen-year figures are better than the over-all survival rate, but not strikingly so. These are 61 per cent, 46 per cent, 31 per cent, and 25 per cent, respectively.

As indicated in the discussion on the pathology of these thyroid cancers, one of the main reasons for attempting to classify them is the recognized variations in behavior of the different histologic types. For example, the papillary tumors are moderately radiosensitive, they invade neighboring structures, and they spread slowly to the regional lymph nodes, but practically never to distant organs by the blood stream. The alveolar adenocarcinomas are more rapidly growing and prone to cause bulky tumors exerting pressure on the trachea and

TABLE XII. OVER-ALL SURVIVAL OF "WELL-DIFFERENTIATED"* THYROID CARCINOMA

YEAR	NUMBER OF CASES	SURVIVAL (YEARS)																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1924	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
1925	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1926	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
1927	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1928	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1929	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1930	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1931	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
1932	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1933	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1934	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1935	3	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	
1936	4	4	4	4	4	4	4	4	4	4	4	3	3	3	3	3	3		
1937	4	3	3	3	3	2	2	1	1	1	1	1	0	0	0	0			
1938	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
1939	2	2	2	2	2	2	2	2	2	2	2	2	2	1					
1940	2	2	2	2	2	2	2	2	2	1	1	0	0						
1941	3	3	3	3	3	2	2	2	2	1	1	1							
1942	2	2	2	1	0	0	0	0	0	0	0								
1943	1	1	1	1	1	1	0	0	0	0									
1944	2	2	2	2	2	2	2	2	2										
1945	3	1	1	1	1	1	1	1											
1946	3	3	3	3	3	3	3												
1947	3	2	2	1	1	1													
1948	7	6	6	6	2														
1949	2	2	2	2															
1950	2	1	1																
1951	4	3																	
1952	1	0																	
Cases	56†	56	55	51	49	47	40	37	34	31	29	28	26	23	21	19	18	14	10
Survival		47	43	39	31	27	24	19	18	14	13	11	9	8	6	5	5	2	1
% Survival		84	78	76	63	57	60	51	53	45	44	39	34	34	28	27	27	14	10

*Benign metastasizing struma, papillary adenocarcinoma, follicular and alveolar adenocarcinoma.

†Fifty-seven cases of well-differentiated thyroid carcinomas, 1 not followed.

esophagus; they are only slightly radiosensitive and metastasize through both lymphatic and blood channels. The spindle or giant cell tumors are consistently radioresistant, metastasize widely, early, and are rapidly fatal. With these facts in mind, it was felt desirable to compare the survival of the well-differentiated lesions in this study with the more poorly or undifferentiated ones. These are shown in Tables XII and XIII. It will be seen immediately that those cases generally considered to be of low malignancy have a prognosis which is vastly more favorable than that of the undifferentiated, highly malignant group. This comparison should serve to remind one of at least two important points. First, in reading about operative results, one must, with carcinoma of the thyroid in particular, consider the histologic frequency of the well-differentiated lesions in any given series. Second, and as a corollary, it would appear that with thyroid cancer, the histology is still the most important factor in prognosis. One cannot deny that many of those cases in the undifferentiated group were well advanced and inoperable when they were first seen. However, in reality many of these cases came to the physician sooner than the slower-growing lesions.

TABLE XIII. OVER-ALL SURVIVAL OF "POORLY DIFFERENTIATED"* CARCINOMA OF THYROID

YEAR	NUMBER OF CASES	SURVIVAL (YEARS)								
		1	2	3	4	5	6	7	8	9
1924	0	0	0	0	0	0	0	0	0	0
1925	0	0	0	0	0	0	0	0	0	0
1926	0	0	0	0	0	0	0	0	0	0
1927	0	0	0	0	0	0	0	0	0	0
1928	0	0	0	0	0	0	0	0	0	0
1929	1	1	1	1	1	1	0	0	0	0
1930	1	0	0	0	0	0	0	0	0	0
1931	0	0	0	0	0	0	0	0	0	0
1932	0	0	0	0	0	0	0	0	0	0
1933	1	1	1	1	0	0	0	0	0	0
1934	2	1	1	0	0	0	0	0	0	0
1935	1	0	0	0	0	0	0	0	0	0
1936	3	0	0	0	0	0	0	0	0	0
1937	3	0	0	0	0	0	0	0	0	0
1938	2	1	1	1	1	1	1	1	1	1
1939	0	0	0	0	0	0	0	0	0	0
1940	2	0	0	0	0	0	0	0	0	0
1941	3	1	1	1	1	1	1	1	1	0
1942	5	1	1	1	1	1	1	0	0	0
1943	1	0	0	0	0	0	0	0	0	
1944	1	0	0	0	0	0	0	0		
1945	4	2	2	0	0	0	0			
1946	2	2	0	0	0	0				
1947	1	0	0	0	0					
1948	4	2	2	0						
1949	2	0	0							
1950	1	0								
1951	2	0								
1952	0	0								
Cases	42	42	42	40	39	37	33	32	30	26
Survival		12	10	5	4	4	3	2	2	1
% Survival		28	24	12	10	10	9	6	6	4

*Solid adenocarcinoma, Hürthle cell, spindle or giant cell, anaplastic unclassified.

There remains in the literature considerable variation of opinion regarding the best surgical management of the most common thyroid cancer precursor, the solitary adenoma. Ward[3] has strongly advocated unilateral total lobectomy

for all solitary adenomas. Lahey,[4] on the other hand, although less dogmatic, feels that simple excision of the nodule is initially sufficient, unless malignancy is suspected either clinically or at surgery. It is a difficult point to settle, and with these ideas in mind 8 cases of solitary adenoma treated by enucleation, but which turned out to be adenocarcinomas on microsection, were followed. No further surgery was performed on these patients either because they refused it or because the pathologist felt that the carcinoma was very small and well circumscribed, and had likely been completely removed. These are tabulated in Table XIV. It will be seen that 3 of the 8 are alive and well. Of these 3, 2 are possibly cured, having each survived sixteen years. All were so-called "low grade tumors." Two additional patients are still alive but have metastases. Admittedly 3 cases are far too few for any conclusion, but nevertheless, might possibly lend support to Ward's contention.

TABLE XIV. RESULTS OF NODULECTOMY FOR MALIGNANT ADENOMAS

PATIENT	DATE	TREATMENT	PATHOLOGIC DIAGNOSIS	FOLLOW-UP
R. N	1931	Nodulectomy	Benign colloid adenoma	
	1936	Nodulectomy and radiation	Papillary adenocarcinoma	February, 1952, alive and well
F. P.	1936	Nodulectomy and radiation	Papillary adenocarcinoma	February, 1952, alive and well
M. M.	1947	Nodulectomy	Metastasizing struma	
	1950	Total thyroidectomy and excision of rib metastasis and radiation	Metastasizing struma	May, 1952, probable lung metastases
B. B.	1948	Nodulectomy and radiation	Papillary cystadenocarcinoma	January, 1952, alive and well
L. A.	1928	Nodulectomy and radiation	Papillary carcinoma	Died January, 1930, due to widespread metastases
H. S.	1952	Nodulectomy and radiation	Follicular adenocarcinoma	September, 1952, alive with metastases
L. O.	1945	Nodulectomy and radiation	Follicular adenocarcinoma	Died, 1946, with carcinomatosis
A. L.	1948	Nodulectomy and radiation	Papillary cystadenocarcinoma	Died, 1951, with metastases

Table XV shows some figures drawn from the literature for comparison. The wide variation is immediately obvious. In 421 patients followed for five years at the Mayo Clinic, Pemberton reported a 61 per cent five-year survival. At the opposite extreme, Watson and Pool reported only a 7.8 per cent five-year survival. Our own figures parallel those of Cole who reported a 38 per cent survival in 1948. The explanation for this variation is difficult to find. In Pemberton's series, 60 per cent of his cases were unsuspected preoperatively or at the time of surgery. Thus in only 40 per cent of his series was the diagnosis made preoperatively. Obviously it would be more difficult to demonstrate satisfactory end results if the clinical diagnosis was more evident in a higher percentage of cases. In our own series, the diagnosis of malignancy was suspected in 58 per cent before surgery. In Watson and Pool's report[14] 70 per cent of their cases were inoperable. A second possibility that suggests itself is that

certain observers might be more lenient in classifying borderline cases as malignant. Finally, one should again recall the rather favorable prognosis in the papillary lesions, which, if constituting a larger proportion of any given series, will certainly boost the five-year survival figure.

TABLE XV. COMPARATIVE[5] RESULTS, FIVE-YEAR SURVIVAL IN THYROID CARCINOMA

AUTHOR	NUMBER OF PATIENTS FOLLOWED FIVE YEARS	FIVE-YEAR SURVIVAL (PER CENT)
Pemberton, Rochester, Minn., 1938	421	61.0
Horn and associates, Philadelphia, Pa., 1947	42	55.0
Cole and associates, Chicago, Ill., 1948	36	38.0
Portmann, Cleveland, Ohio, 1940	149	35.5
De Quervain, Switzerland, 1935	108	17.5
D'Argent, Lyon, France, 1941	135	9.6
Watson and Pool, New York, N. Y., 1940	167	7.8
University of Minn. Hospitals, Minneapolis, Minn., 1952	84	37.0

As regards comparative figures in those cases where patients were treated by thyroidectomy, those reported by Pemberton[8] should be mentioned. Thus, of patients who underwent a thyroidectomy with or without radiation, he reported a three-, five-, and ten-year survival of 77 per cent, 70 per cent, and 58 per cent, respectively. Our own figures as shown in Table XI were 61 per cent, 46 per cent, and 31 per cent, respectively, for the same time intervals.

SUMMARY

1. One hundred one cases of thyroid malignancy seen and treated at the University Hospitals from June, 1924, to June, 1952, are reviewed.

2. Over one-third (35 per cent) of the cases presented with metastases on their initial visit.

3. In a high percentage of those cases where the diagnosis of malignancy was not obvious, the clinical description and assessment of the lesion were inaccurate.

4. The mean duration from onset of the lesion to treatment was sixty-eight months.

5. Ten per cent of the patients showed clinical and laboratory evidence of hyperthyroidism.

6. The manner in which these patients were treated is outlined. The operability rate for the entire group was 63.3 per cent. A majority of the patients received deep x-ray therapy.

7. The percentage of cases suitable for isotope therapy was similar to that of other reported series.

8. The over-all survival for rates for three, five, ten, and fifteen years was 47 per cent, 34 per cent, 24 per cent, and 14 per cent, respectively.

9. Of those patients who underwent thyroid surgery (usually with irradiation) the three-, five-, ten-, and fifteen-year survival rates were 61 per cent, 46 per cent, 31 per cent, and 25 per cent, respectively.

10. The histologic nature of the tumor remains an important factor in the prognosis.

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VILLOUS PAPILLOMAS OF THE COLON AND RECTUM

A Study of Twenty-Eight Cases With End Results of Treatment Over a Five-Year Period

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THE distinctive morphology of a group of tumors has resulted in their descriptive classification as "villous papillomas" of the colon and rectum. Holmes,[1] a British pathologist, originated use of the term "villous tumor" in 1860, thus dividing benign epithelial tumors of the large bowel into two categories, the villous papilloma and the adenomatous polyp. This concept has proved useful to the clinician as an aid in classification, and the concept is believed to be substantiated by morphologic, pathologic, and clinical features which tend to demarcate this type of intestinal neoplasm from the more commonly appreciated adenomatous polyp to which it is closely related.

Villous papillomas are not confined entirely to the large bowel, although the colon and rectum constitute the site of most common occurrence. Hauser[2] in 1890 described villous tumors of the stomach. Villiform papillomas of the gall bladder have been encountered. Among the earliest to describe villous papillomas of the rectum were Quenu and Landel,[3] Lambling,[4] and Bensaude.[5]

As Dukes[6] has pointed out, both varieties of benign epithelial tumor arise from mucous membrane, but the adenoma is typically a compact, spherical, pedunculated mass while the villous papilloma is typically a soft, sessile tumor without pedicle. The adenoma is common, occurring in 7 per cent of adults, according to Helwig,[7] while the papilloma is a rare tumor. Villous papillomas are often referred to as papillary adenomas, but differences in cancer potential, morphology, and clinical behavior tend to differentiate true papilloma and true adenoma. All villous papillomas may be described as papillary, but not all adenomas are papillary, for the adenomas have preponderantly a typical, pedunculated configuration, except for the smooth embryonic forms recognized as mammillations of only several millimeters in size. The soft, velvetlike consistency and broad sessile arrangement of villiform projections identify the villous papilloma in striking contrast to all other tumors of the distal bowel.

The purpose of this study is to present differential criteria which have been useful in diagnosis and managment of villous papillomas over a five-year period.

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MATERIAL AND METHODS

The twenty-eight cases* were selected from a total of 1,144 tumors of the colon and rectum treated during a five-year period from November, 1946, to December, 1951. This series excluded all tumor-simulating lesions of the colon and rectum which were of inflammatory or granulomatous nature unassociated with neoplasm. For comparative purposes, it may be stated that of these 1,144 tumors, the most common was adenocarcinoma, comprising 69 per cent of the total, while benign epithelial tumors, or "polyps," made up 23.7 per cent of the total. The remaining 7.3 per cent included uncommon tumors such as lymphoma, sarcoma, carcinoid, fibroma, endometrioma, hemangiopericytoma, and others.

Of the benign epithelial tumors, consisting of 272 cases, it was found that the adenoma accounted for 21.4 per cent of the total (243 adenomas) while the villous papilloma was found in 28 cases, or 2.3 per cent of the total number of 1,144 tumors.

Determination of the incidence of villous papilloma was based on these primary considerations: (1) villous configuration, (2) broad, sessile base without pedicle, (3) predominantly benign morphology, (4) soft consistency, free of ulceration or induration, and (5) freedom of fixation to the underlying muscularis layer of the bowel. Additional secondary considerations excluded those tumors whose surface was only coarsely lobular or those tumors having a gross papillary surface but failing on microscopic examination to possess true villous processes. Only those tumors were included which did not appear clinically to present any evidence of carcinoma, or microscopically did not show diffuse carcinomatous change. Tumors were included whose structure, except for microscopic foci of cytologic carcinoma (in situ), was otherwise benign.

Thus it was found that 28 of 1,144 tumors sufficiently satisfied these criteria to permit their classification as villous papillomas in contradistinction to either adenomatous polyps or well-differentiated papillary adenocarcinomas. Adenomatous polyps having a variable papillary appearance of their outer pole, away from their pedunculated base, were similarly excluded. Features of the architectural pattern of villous papillomas described by Dukes,[6] Gabriel,[8] and Ewing[9] have been helpful in differentiating these tumors. Sunderland and Binkley[10] and recently Fisher and Castro[11] have described a group of papillary adenomas, and it has been reiterated that papillary adenomas are growth variants of the same process that produces the adenomatous polyp. Which term better identifies these varieties of epithelial bowel tumors is a matter of individual preference, as long as appreciation exists that the villous papillomas present a striking morphologic pattern apart from the more common adenoma.

*Two additional patients, making a total of 30 cases, have recently undergone resection for villous papilloma, but too recently to be included in the follow-up of this series.

PATHOLOGY

The identifying gross pathologic features of the villous papilloma include (1) villous configuration, (2) broad, sessile base without pedicle, (3) soft, velvety consistency without ulceration or induration, and (4) mobile, superficial disposition without fixation. The tumor is pale and reddish gray in color, and usually extends over a wide area of bowel mucosa ranging from 4 to 5 cm. in area to complete circumferential involvement as shown in Figs. 1 and 2. Frequently there is a viscid coat of mucus, secreted in liberal amounts by the tumor and accounting for its most classic symptom.

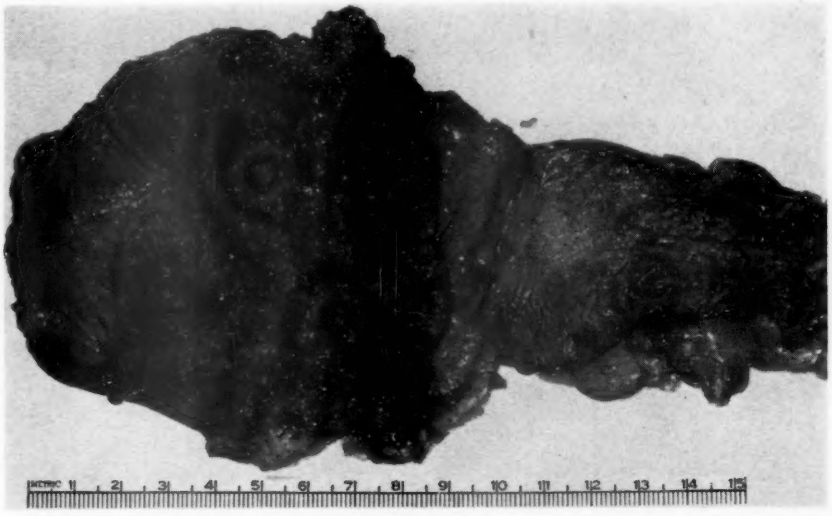

Fig. 1.—Villous papilloma of rectosigmoid in A. M., a 58-year-old woman.

Fig. 2.—Villous papilloma of rectum with carcinomatous change in A. H., a 69-year-old woman.

The identifying microscopic features found most helpful in diagnosis are (1) innumerable elongated fingerlike projections, covered by surface epithelium and having a core of connective tissue stroma, small vessels, and occasional nerve fibers, (2) typical goblet cells of mucosa, although there is no remarkable increase in their number and there is no striking increase of dense glandular acini, (3) normal-staining nuclear and cytoplasmic components, un-

less there are isolated, focal areas of what is described as "carcinoma in situ." Thus, the histologic structure is essentially and predominantly benign, in the classic example, without increased mitoses, hyperchromaticity, architectural derangement, lack of differentiation, or depolarization, and (4) a characteristic limitation to the superficial mucosal layer without evidence of cellular invasion through the lamina propria to the muscularis.

The histopathologic factor of greatest aid in diagnosis of this tumor is the presence of elongated villous processes with the relative absence of compactly arranged glandular elements, as demonstrated in Fig. 3; when these features are apparent, as in the typical case, distinction may be made from the typical adenomatous polyp, which is being detected and removed with increasing frequency.

The increased mucoepithelial surface, rather than the glandular elements, as reflected in the villous configuration, illustrates the theory advanced by Dukes[6] that the villous papilloma is the end result of a growth pattern which has affected mainly the superficial epithelium in contrast to the adenoma which is the result of a growth pattern affecting mainly those cells at a deeper level.

Metastases to the reginal lymph nodes or extension to other viscera appear to be uncommon, even when isolated foci of the villous tumor demonstrate malignant change.

CLINICAL FEATURES

Symptomatically, villous papilloma may be confused with "mucous colitis," for in the classic example of this tumor, elaborating increased mucus, the patient notes mucus discharges from the rectum, unassociated with other complaints. Other symptoms include rectal bleeding, altered bowel habit, more frequently toward diarrhea than toward constipation, and protrusion of tissue fragments.

Of the twenty-eight patients studied, bleeding occurred in 78.5 per cent, diarrhea in 46.4 per cent, mucoid discharges in 31.4 per cent, and protrusion of tumor in 21.4 per cent. Constipation occurred in 17.8 per cent and weight loss in 14.3 per cent, while 7.1 per cent complained of pruritus and 3.6 per cent complained of rectal pain. Of the twenty-eight patients, 17.8 per cent were free of symptoms, indicating that the villous papilloma may be a silent tumor; in these asymtomatic patients, almost one-fifth of the series, discovery of the lesion was made as a result of routine proctosigmoidoscopy.

Length of symptoms varied from one week to fifteen years, the average being fifteen months. One patient having symptoms of fifteen years' duration had been erroneously treated for mucous colitis.

Age of the patients ranged from 23 to 74 years, the average age being 55.4 years. Sunderland and Binkley[10] reported the average age of forty-eight patients having papillary adenomas to be 62.9 years, while adenomatous polyps are variously reported in the range of from 45 to 54 years. Thus, it would

appear that villous papillomas tend to occur in a slightly older age group than the adenomas.

Sex incidence paralleled that of adenomas, being 56 per cent for male patients and 44 per cent for women, in this study.

Fig. 3.

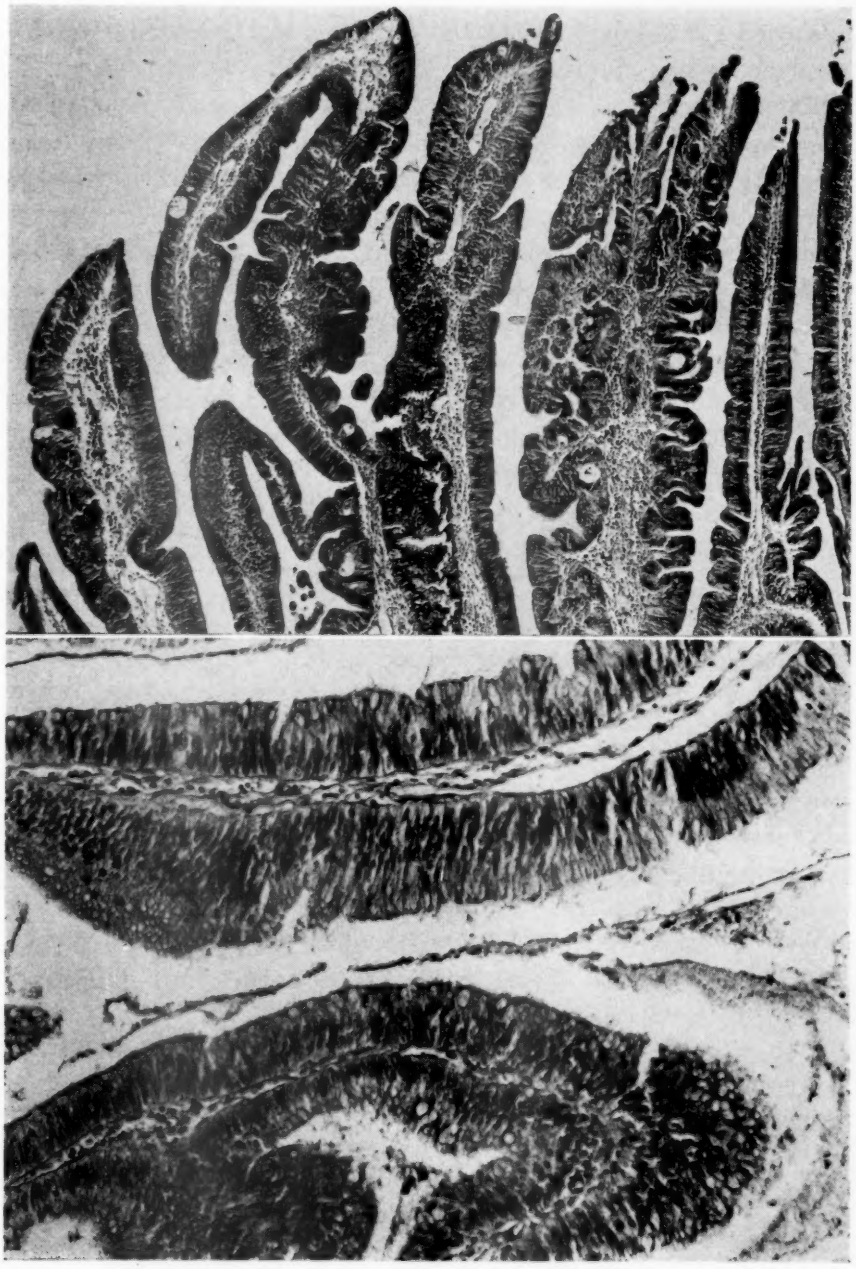

Fig. 4.

Fig. 3.—Typical microscopic appearance of villous papilloma (×40, reduced ⅓) in O. L., a 59-year-old man.

Fig. 4.—Villous papilloma with areas of atypism in C. H., a 71-year-old man.

The appearance of the tumor is that of a villiform, sessile configuration composed of pale, reddish gray rows of mucosa. When within reach of the examining finger, the classical villous papilloma frequently escapes notice because of its innocuously soft texture, as emphasized by Gabriel[8] and others, and even on direct sigmoidoscopic visualization it may escape attention as the sigmoidoscope flattens its pliable, resilient pattern.

Size varied from 2 by 5 cm. to 10 by 18 cm., the largest in circumference; the average size was found to be approximately 6 by 12 cm.

Site of occurrence for the majority of these tumors was below the level of the peritoneal reflection, for example, in the rectum, twenty-two of the twenty-eight tumors occurring at or below the rectosigmoid junction (78.5 per cent) and 6, or 21.5 per cent, occurring above the level of the peritoneal reflection, for example, the sigmoid colon or higher.

Position of the tumor with reference to the lumen of the bowel was found to be almost or completely circumferential in 39.2 per cent or eleven of the twenty-eight cases, mainly anterior in 21.5 per cent (six cases), mainly anterolateral in 25 per cent (seven cases), posterolateral and lateral, respectively, in 7.1 per cent (two cases), demonstrating a preference for origin in the anterior and lateral phases of the lumen.

The proximalmost tumor occurred in the transverse colon, although Fisher and Castro[11] have reported occurrence of villous papilloma in the ascending colon.

Associated, incidental, typically pedunculated adenomatous polyps were found in three of the twenty-eight patients, or 10.7 per cent, the adenomas being located an appreciable distance away from the villous tumor; associated, separate adenocarcinoma, occurring synchronously with the villous papilloma, was found in two of the twenty-eight patients, or 7.1 per cent.

Liver involvement, as noted on abdominal exploration, was demonstrable in 7.1 per cent, or two of the twenty-eight patients; in these two patients areas of low-grade papillary adenocarcinoma were found on subsequent pathologic study of the lesion; both occurred in the lower rectum, and both of these patients are alive two and one-half years following a Miles-type procedure, with abdominal colostomy. Lymph-node involvement was present in one of the twenty-eight cases, or 3.6 per cent.

HISTOPATHOLOGIC FEATURES

The twenty-eight villous papillomas were analyzed with respect to histologic patterns. Fig. 3 illustrates the representative pattern found in eighteen of the twenty-eight lesions, or 64.3 per cent, classified as benign villous papilloma. The remaining 35.7 per cent were classified as showing malignant changes.

Further analysis revealed the following: seven of the twenty-eight tumors (25 per cent) were designated as classical benign villous papilloma without evidence of cellular changes; six of the twenty-eight tumors (21.5 per cent) were designated as showing "adenoma malignum" change in addition

to the basic architecture, while five of the twenty-eight, or 17.1 per cent, received the analogous term now in use—atypism. These two qualifications, adenoma malignum and atypism, have been employed to designate the near-malignant changes of hyperchromatism, stratification, nuclear and cytoplasmic irregularities without actual immaturity, and lack of differentiation or of invasiveness. The term adenoma malignum was used formerly to designate changes which are now being described as atypism and represent the same histologic findings, which, however, do not qualify as actual carcinomatous change, whether diffuse or in situ. Thus eleven of the twenty-eight lesions, or 38.6 per cent, showed changes of atypism if the later terminology were applied to all of such cases as illustrated in Fig. 4.

However, in five of the twenty-eight tumors, or 17.1 per cent, one or more focal, limited areas were found satisfying the qualification of localized adenocarcinoma in situ, as illustrated in Fig. 5, and in four of the twenty-eight tumors, areas of unconfined papillar, well-differentiated "low-grade," or Grade I, adenocarcinoma were present (14.3 per cent), as illustrated in Fig. 6. Thus, nine of the twenty-eight villous papillomas, or 35.7 per cent, without gross or preoperative evidence to biopsy or other means, were found to contain either focal adenocarcinoma or proliferating areas of well-differentiated, papillary adenocarcinoma. The percentage of malignant degeneration found in villous tumors has been reported by Sunderland and Binkley[10] as 68 per cent, and by Ewing[9] as from 10 to 20 per cent. More recently, Fisher and Castro[11] by serial section reported four cases of papillary adenoma to have demonstrable areas of adenocarcinoma in 100 per cent, while Welch, McKittrick, and Behringer[12] have shown that malignancy is demonstrable in 22 per cent of papillary villous tumors as compared to 17 per cent in pedunculated adenomas.

TREATMENT AND RESULTS

Wide removal of the lesion was carried out in twenty-six of the twenty-eight patients (92.9 per cent), while in two patients of the twenty-eight (7.1 per cent) a localized Bevan-type excision of rectal mucosa was employed. Specific types of procedure were based on location of the lesion and routes of lymphatic spread for malignant lesions of the large bowel. Thus lesions occurring at or below the lateral ligaments of the rectum, corresponding to Kohlrausch's plica, that is, 7 cm. above the anus, were treated by extended Miles excision of the rectum with abdominal colostomy, while lesions occurring above the zone of lateral spread but below the lower sigmoid (that is, 7 to 15 cm. above the anus) were treated by abdominoperineal proctosigmoidectomy with sphincter preservation, as shown by the abbreviation APPS in Table I. Lesions in the sigmoid colon, presenting adequate segment of bowel for anticipated cure without recurrence by resection, were treated by sigmoidectomy; the APPS has proved to result in removal of more extensive length of bowel in the treatment of upper rectal or "rectosigmoidal" lesions than permitted by low anterior resection, which is admittedly accompanied by the risk of malignant cytologic exfoliation and greater possibility of recurrence than with a more radical pro-

cedure, when performed for other than palliative purpose. Resection, then, was mainly restricted to lesions above the upper rectum, for example, sigmoid, and, for one lesion occurring in the transverse colon, with end-to-end anastomo-

Fig. 5.

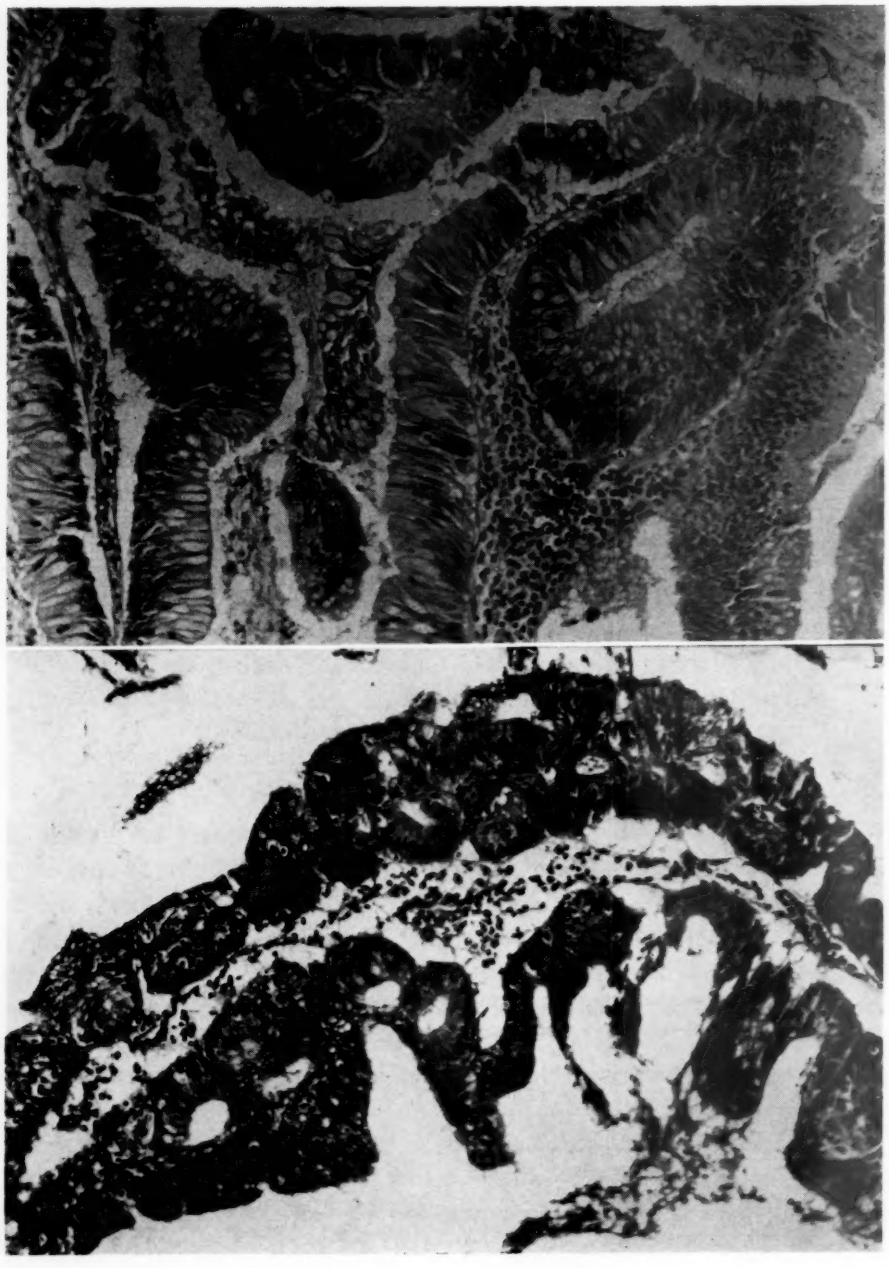

Fig. 6.

Fig. 5.—Villous papilloma with area of adenocarcinoma in situ (×200, reduced ⅓) in A. M., a 58-year-old woman.

Fig. 6.—Villous papilloma with carcinomatous change but without invasion of muscularis; superficial adenocarcinoma, well differentiated in A. H., a 69-year-old woman.

sis; all procedures included removal of contiguous mesentery, including lymph nodes and vascular pedicle ligation up to the origin of the inferior mesenteric artery from the aorta, except for the two instances where Bevan excision was indicated. The treatment is summarized in Table I, along with results.

TABLE I. TREATMENT AND RESULTS

PERIOD OF TIME FOLLOWING SURGERY IN WHICH PATIENTS ARE ALIVE AND WELL (YEARS)	TYPE OF PROCEDURE EMPLOYED AND NUMBER OF PATIENTS				
	APPS*	MILES	SIGMOIDECTOMY	RESECTION TRANSVERSE COLON	BEVAN EXCISION
1-2	3	2	2	0	1
2-3	1	1	0	1	1
3-4	3	1	1	0	0
4-5	2	1	0	0	0
5-6	5	1	1	0	0
6-7	1	0	0	0	0
Known liver involvement	0	2	0	0	0
Deaths	1†	1	0	0	0
Unavailable for follow-up	1‡	0	0	0	0
Known recurrence	1§	0	0	0	0
Total of patients living	14	5	4	1	2
Total patients	15	6	4	1	2

*Abdominoperineal proctosigmoidectomy.

†Death due to recurrent gastric carcinoma as revealed by autopsy.

‡Alive at last follow-up two years previously; moved to another state.

§Patient had multiple malignancy, adenocarcinoma of rectum, causing recurrence, in addition to villous papilloma of splenic flexure, with carcinomatous degeneration; lymph-node studies had revealed unfavorable prognosis following surgery, despite any procedure.

Of the twenty-eight patients treated, and followed for a period of time ranging from two to seven years, there have been no deaths attributable to the tumor per se; two patients have died from incidental causes; one patient died from cerebrovascular accident eight months following discharge from the hospital, while in the other patient death occurred ten months following gastrectomy for an adenocarcinoma of the stomach discovered and treated incident to removal of the rectum for a villous papilloma with carcinomatous change; autopsy in this instance revealed death due to recurrence of gastric carcinoma.

The prognosis in three patients now living is unfavorable because of liver involvement noted at the time of surgery in two patients and known recurrence from a simultaneously occurring and treated adenocarcinoma of the rectum in addition to a villous papilloma of the splenic flexure. Of the two patients with liver involvement, one is alive two and one-half years following surgery, and the other now living three and one-half years following surgery, both patients having had a Miles operation for a villous papilloma with carcinomatous degeneration in the lower rectum, of Dukes or Bormann Type 1 lesion.

SUMMARY AND CONCLUSIONS

Benign epithelial tumors, arising from mucous membrane, represent the most common tumors of the colon and rectum and may be classified into two groups. The more common, originating as a mucosal mammillation, is recognized as the adenomatous polyp, which is typically a compact, pedunculated mass, usually smooth but often having a papillary arrangement of the luminal

pole and which occurs in approximately 7 per cent of all adults. The other less commonly occurring lesion appears as a broad, sessile velvetlike tumor with soft villous projections in striking morphologic contrast to all other benign or malignant tumors of the large bowel. The descriptive classification of villous papillomas, often referred to as papillary adenomas, has been useful to the clinician in recognizing certain morphologic, pathologic, and clinical features tending to demarcate this tumor from the closely related adenomatous polyp. Villous papillomas often present a problem, for repeated biopsies may be consistently benign and the lesions present no opportunity for well-defined local excision or electrodesiccation commonly presenting with the adenomatous polyp or mammillation.

Based on the study of 1,144 benign and malignant tumors of the large bowel, over a five-year period from 1946 to 1951, twenty-eight villous papillomas were encountered, representing an incidence of 2.3 per cent of the total, compared to adenomatous polyps having an incidence of 21.4 per cent. In this series, adenomatous polyps were ten times as common as the villous papilloma. Criteria for the villous papilloma have been described. According to Dukes, the villous papilloma is the end result of a growth pattern affecting mainly the superficial epithelium rather than cells at a deeper layer giving rise to the adenoma.

Symptomatology and clinical features have been presented. Analysis of the histopathologic features reveals that evidence of adenocarcinoma was present in 35.7 per cent of villous papillomas in this series, in the absence of any induration or other finding to suggest malignancy. In contrast, adenocarcinomatous change is found in 15 to 19 per cent of adenomatous polyps.

Follow-up study on twenty-eight having undergone surgery from 1946 to 1951 reveals the over-all survival rate to be 92.9 per cent over a period ranging from two to seven years at the time of concluding this study. Eleven patients, or 39.3 per cent, have survived five or more years, while the remainder are at present in the two- to five-year group. The prognosis has been found more favorable in those patients in whom no evidence of carcinomatous foci was demonstrable, and more favorable in those patients whose lesions were above the level of Kohlrausch's plica or lateral ligaments of the rectum.

Recognition of villous papilloma, from the criteria described, and appreciation of its tendency toward malignant behavior present indication for adequate extirpation of involved large bowel and areas of lymphatic drainage despite ostensibly benign pathology.

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CONSECUTIVE SURVIVAL OF OPEN-CHEST, HYPOTHERMIC DOGS AFTER PROLONGED BY-PASS OF HEART AND LUNGS BY MEANS OF A PUMP-OXYGENATOR

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THE idea of substituting a mechanical device for the function of the heart and lungs is by no means new. Le Gallois wrote in 1812: "If one could substitute for the heart a kind of injection of arterial blood, either natural or artificially made, one would succeed easily in maintaining alive indefinitely any part of the body whatsoever."[1] In spite of the great interest and definite advances in this field in recent years, the statement must still be considered overoptimistic since the most enthusiastic investigator of today would hardly state that he succeeds "easily" in keeping animals alive even for short periods of time by artificial devices.

The literature has been extensively reviewed by Björk,[2] Dennis,[3] and Miller,[4] but many substantial contributions from abroad[5-9] have not been given sufficient attention in this country.

The first mammal, a cat, which survived clamping of the pulmonary artery for thirty minutes, was reported by Gibbon in 1937.[10] The first series of consecutive survivals of thirteen dogs in which the entire blood flow was diverted from the heart and the lungs was achieved by Gibbon and his associates last year.[11] These investigators have been pioneers in the perfection of a blood-film-type oxygenator, and the continuity of at least sixteen years of experimental effort has been rewarded by the first successful clinical application.[12]

The present communication describes experiences with a pump-oxygenator based on the principle of gas dispersion.[13, 14] The efficiency and safety of this instrument have been tested previously in the prevention of acute anoxic anoxia[15] and in the exclusion of heart and lungs from the circulation of hypothermic "closed-chest" dogs.[16] Although all dogs whose chests were not opened survived the by-pass of heart and lungs, dogs with thoracotomies showed a high mortality when subjected to the same procedure.[17] It seemed probable that inadequate neutralization of the heparin effect after thoracic surgery was the major obstacle to survival.

MATERIALS AND METHODS

Operative Procedure.—Dogs are anesthetized with 50 mg. of Nembutal per kilogram, and the right jugular vein and both femoral arteries and veins are prepared for cannulation. After the injection of 10 mg. of heparin per kilogram, polyethylene catheters with longitudinal slits are introduced into the

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veins for the withdrawal of blood from the caval system to the pump-oxygenator. Long polyethylene tubes for the return of the oxygenated blood from the instrument are introduced into the femoral arteries and advanced far enough to reach the aortic arch. The right carotid artery is connected to a mercury manometer.

A thoracotomy through the right fourth intercostal space is performed under strictly aseptic conditions. Cutting, as well as meticulous hemostasis, is performed with the Bovie electrosurgical unit exclusively. No delay of wound healing and no increased incidence of morbidity have been noted. Positive pressure aeration of the lungs is achieved with an endotracheal tube and a mechanical air respirator, employing an air-tight system.

The vena azygos is ligated, and the superior and inferior venae cavae are mobilized for later occlusion with rubber-dam tapes. When satisfactory blood flow, oxygenation, and hypothermia are achieved by the pump-oxygenator the respirator is shut off, and the venae cavae are occluded by tightening the rubber tapes and holding them in place with bulldog clamps. Hypothermia can be rapidly produced by cooling the blood in the extracorporeal circulation by means of a silver or stainless steel coil immersed in ice water.[18]

When the perfusion is over the occlusive tapes are released, the respirator is started, and the pump-oxygenator is stopped. This can be done abruptly since the heart takes over from one beat to another without any evidence of electrocardiographic change.

The thoracotomy incision is carefully closed in anatomic layers about a thoracotomy tube connected to constant water suction, and the animal remains on the table under observation for the next four to five hours. Observation of the blood pressure is continued until normal coagulation time is restored, and artificial respiration is continued until shivering appears (at a rectal temperature of about 30° C.). The thoracotomy tube is also removed at this time. It is preferable to raise the body temperature slowly by means of heating pads in order to prolong the period of hypothermic low-oxygen requirement immediately following the closure of the chest cavity. The rate and volume of the respirator should be reduced during this time in order to avoid respiratory alkalosis. When shivering has begun, the animal may be placed in the cage. Subsequent postoperative care consists of the administration of antibiotics for five days and the maintenance of adequate nutrition.

Neutralization of Heparin.—Two to five milligrams of heparin are sufficient to keep the blood incoagulable in any of the blood-film-type oxygenators, but a minimum of 10 mg. of heparin per kilogram is needed to prevent fibrin embolism in the gas-dispersion-type oxygenator used in these experiments.

In sixty-eight heparinized dogs, clotting-time determinations in siliconed tubes and protamine-heparin titrations were carried out during the first two postoperative hours. Six different routines of immediate postoperative management of the heparin-induced clotting defect were tested: (1) administration of a dose of Protamine Sulfate equivalent to the heparin which had been given; (2) administration of one-half the equivalent amount of protamine; (3) slow

transfusion with 300 to 500 ml. of citrated blood; (4) administration of one-half the equivalent amount of protamine followed by a transfusion of citrated blood; (5) administration of one-half the equivalent amount of protamine, slow intravenous injection of 1 Gm. of calcium gluconate, and then a transfusion of citrated blood; and (6) administration of one-half the equivalent dose of heparin followed by a transfusion of fresh or decalcified blood.

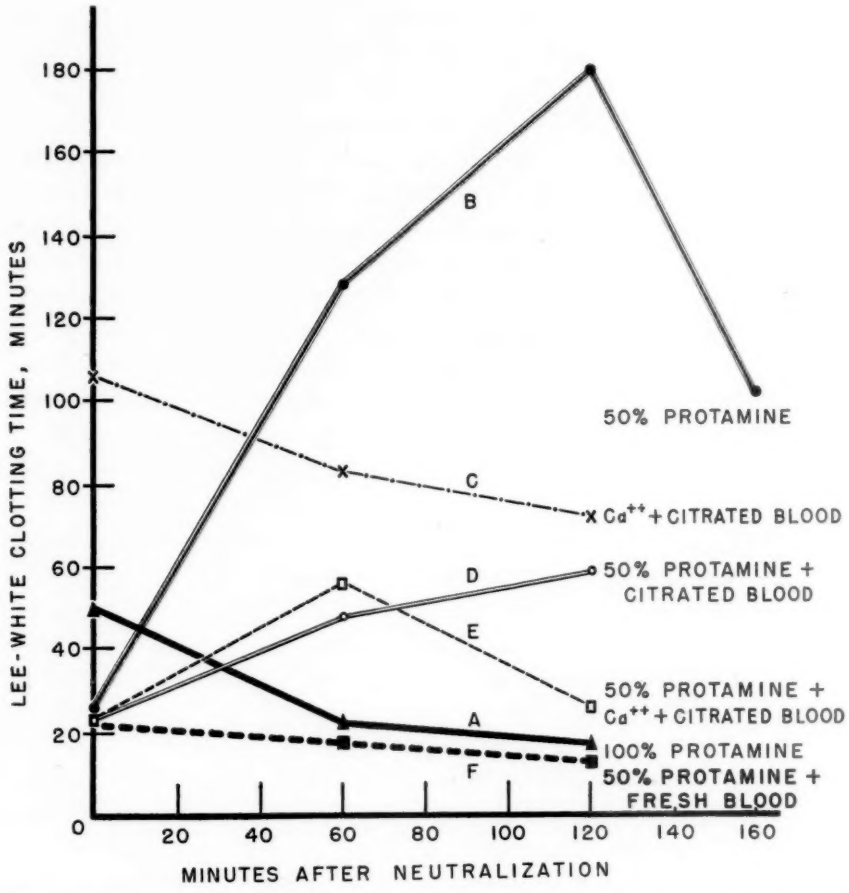

Fig. 1.—Neutralization procedures of heparin after the use of a pump-oxygenator.

If each milligram of heparin is covered with an equal amount of protamine, clotting time remains prolonged for about one hour (Fig. 1, *A*). Covering one-half of the injected amount of heparin with protamine rapidly restores the clotting time to normal. This situation, however, is not stable under our experimental conditions, and a prolongation of clotting time occurs again which reaches its maximum after one to two hours (Fig. 1, *B*). During this time increasing amounts of protamine are needed to bring the clotting time back to normal in heparin-protamine titrations (Fig. 2). Such titrations were found too cumbersome for routine use. Attempts were therefore made to preserve the initial benefit of the one-half dose of protamine by the transfusion of blood. The results of this procedure (Fig. 1) show that neither calcium gluconate and

citrated blood (*C*) nor one-half the dose of protamine followed by a transfusion of citrated blood with (*E*) or without (*D*) calcium gluconate is capable of restoring normal blood clotting at all times after the experiment.

The only procedure which achieves this goal is the administration of one-half the equivalent dose of protamine followed by a transfusion of 300 to 500 ml. of fresh or decalcified blood (*F*). With this technique of heparin neutralization, postoperative prolongation of clotting time was prevented and all hemorrhagic complications were eliminated.

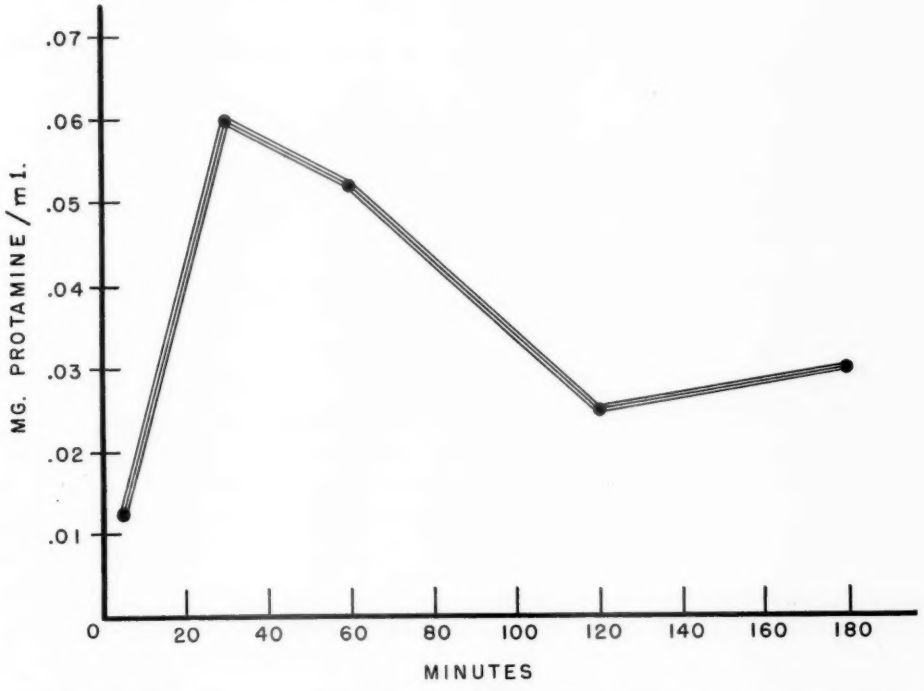

Fig. 2.—Fifty per cent protamine titration of heparinized blood to five minutes' clotting time. (Each point represents the average of ten experiments.) Heparin-protamine: Titration in 1 ml. blood samples after intravenous administration of one-half the equivalent amount of protamine.

Blood Changes During Perfusion.—The maintenance of satisfactory oxygen saturation, pH, and carbon-dioxide content by the use of this instrument has been reported previously.[13, 17] Hemolysis is minimal even after prolonged pumping.[14] The present study encompasses changes in the hematocrit, red blood count, white blood count, platelet count, eosinophil count, and vitamin C blood level. Changes in the corpuscular elements are due to the effect of filling the instrument with heparinized donor blood diluted with 5 per cent glucose in saline solution and to destruction of cells that has occurred during the perfusion (Fig. 3). Hematocrit and red cell count show the dilution effect at the end of the perfusion, but the transfusion of fresh or decalcified blood raises their level somewhat higher than the preperfusion value. The destruction of platelets during the procedure is evident from reduction to less than one-half the original value at the end of the perfusion. The blood transfusion, however, returns the

platelet count to a safe level. Even more severe is the drop in the white cell count at the end of the perfusion to about one-fourth of the original count. Again, the blood transfusion at the end of the procedure returns the total white blood count to a normal level. In contradistinction to all other cell elements studied, the eosinophil cell reduction after the perfusion is not brought back to normal by a subsequent blood transfusion. Table I shows the mean percentage change from the control value, as well as the difference from the red cell count.

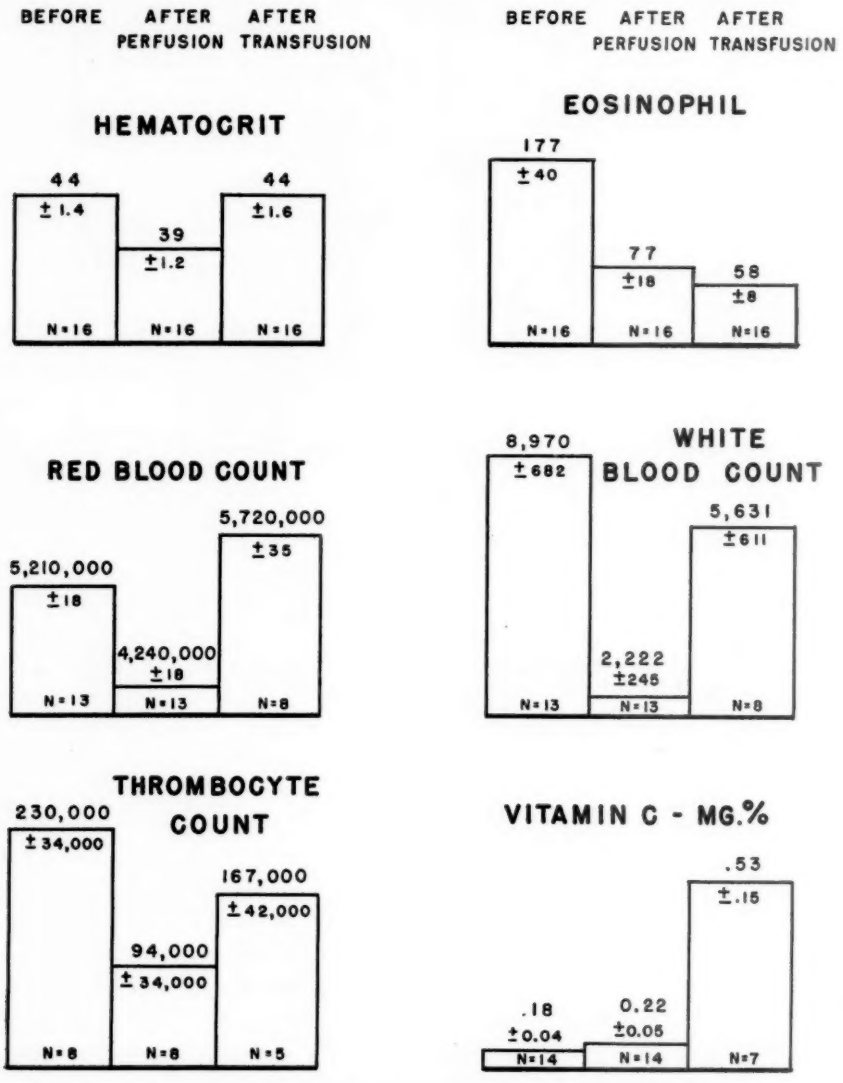

Fig. 3.—Blood changes after perfusion and after transfusion.

Preliminary tests have shown that vitamin C disappears from blood in about fifteen minutes when oxygen dispersed by sintered glass bubbles through it. The question arose as to whether the hemorrhagic manifestations after the perfusion might be due to an acute deficiency of ascorbic acid produced by the prolonged dispersion of fine oxygen bubbles in blood. The results of blood

vitamin C determinations in these animals show that the changes during the perfusion are insignificant and that transfusion of fresh or decalcified blood raises the vitamin C to about three times the control level.

TABLE I. MEAN PERCENTAGE OF CHANGE FROM CONTROL VALUE TO VALUE AT END OF THIRTY-MINUTE PERFUSION

	NUMBER OF DOGS	MEAN PERCENTAGE ± STANDARD ERROR	DIFFERENCE FROM RED BLOOD COUNT (MEAN PERCENTAGE OF CHANGE)	PROBABILITY
Red blood count	13	−17 ± 3		
White blood count	16	−72 ± 4	55	.001
Platelet	8	−54 ± 7	37	.001
Eosinophils	16	−48 ± 7	33	.01

Physiologic Observations.—Measurement of carotid blood pressure, blood flow through the instrument, respiratory rate, and rectal temperature during the exclusion of heart and lungs are recorded in Table II. Seventeen consecutive dogs of 15 to 28.7 kilograms in weight were perfused from twenty-seven to sixty minutes. Fifteen survived the procedure without any ill effects and were observed for about one month. Dog 2 died of acute anoxia due to a leak in the rubber cuff of the endotracheal tube during the closure of the thoracotomy. Dog 11 walked around the day after the experiment, but appeared weak and did not drink. A subcutaneous infusion of 5 per cent glucose was given at a rapid rate by the addition of hyaluronidase. At the end of the infusion the animal collapsed and died. An autopsy was negative and no blood was found in the chest cavity; the cause of death was attributed to electrolyte shock due to too rapid subcutaneous infusion of glucose.[19]

TABLE II

DOG	WEIGHT (KG.)	BLOOD FLOW (C.C./KG./MIN.)	RECTAL TEMPERATURE (° C.)	BLOOD PRESSURE (MM. Hg)	RESPIRATORY RATE (PER MIN.)	DURATION OF BY-PASS (MIN.)	OUTCOME	LENGTH OF OBSERVATION (DAYS)
1	19.0	55	27.5	100/60	4	27	Lived	32
2	20.0	50	26.5	100/50	2	30	Died	1
3	15.5	45	25.0	40/35	0	30	Lived	23
4	21.5	40	26.5	90/60	0	32	Lived	33
5	27.3	41	27.0	90/50	–	35	Lived	29
6	23.6	35	25.0	80/40	–	30	Lived	28
7	18.6	47	26.0	90/50	0	35	Lived	28
8	16.4	50	27.0	90/50	8	31	Lived	27
9	28.7	46	27.0	70/40	2	31	Lived	31
10	19.5	45	27.0	100/50	0	30	Lived	27
11	15.0	54	24.0	55/20	10	30	Died	1
12	22.2	38	24.0	40/20	0	60	Lived	28
13	21.3	33	25.0	80/50	0	31	Lived	32
14	16.8	68	24.0	100/50	0	30	Lived	28
15	21.3	53	25.0	90/40	2	60	Lived	28
16	18.1	65	27.0	90/40	0	32	Lived	30
17	23.0	35	26.0	80/40	0	57	Lived	32

Blood pressure, blood flow, and respiratory rate at the prevailing low body temperature can be evaluated only if compared with the physiologic values for

the corresponding degree of hypothermia. Fig. 4 indicates that the blood flow reached corresponded in most cases to the cardiac output of hypothermic animals as determined by Bigelow and associates.[20] Even such low flow rates as 30 to 40 c.c. per kilogram per minute at 25° C., as compared with 130 to 150 c.c. per kilogram per minute at normal body temperature, are sufficient to supply the brain with enough oxygen. It should be added, however, that this holds true only if the blood pressure in the cerebral circulation is kept at a much higher level than is physiologic at these low body temperatures. Fig. 5 shows that the location of the arterial catheters high up in the aorta resulted generally in carotid blood pressure materially higher than in dogs of the same degree of hypothermia with the catheters placed more distally.[20] In previous experiments, for example, we have seen brain damage result if, at such a low blood flow rate, the arterial cannulae were placed in the femoral arteries. In such instances, the carotid blood pressure equaled the "physiologic" hypothermic values as reported by Bigelow and co-workers.[20]

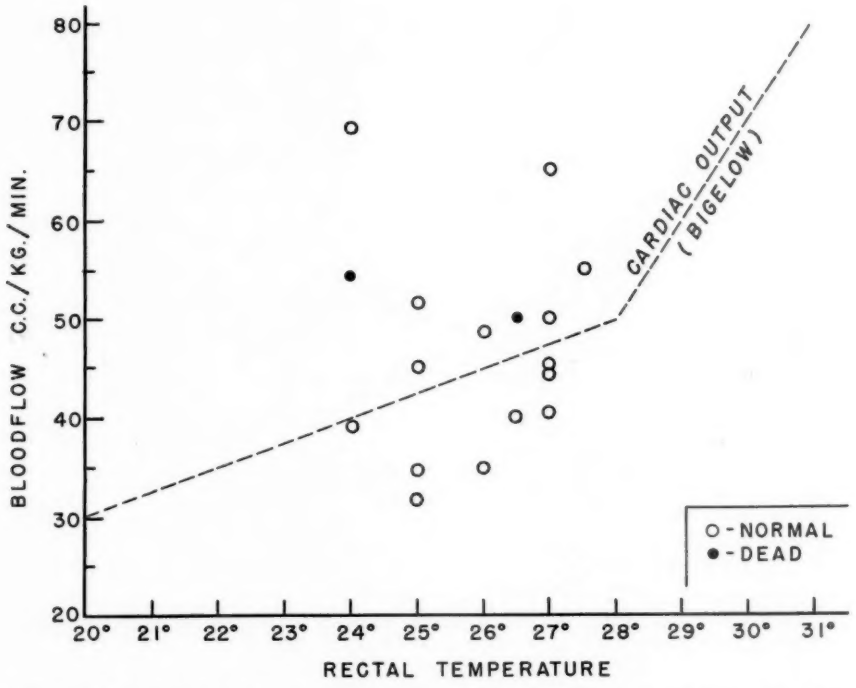

Fig. 4.—Blood flow in the pump-oxygenator during total by-pass of heart and lungs in hypothermic, open-chest dogs.

The fact that we actually overoxygenated the brains of all but two animals can be seen in Fig. 6 where the recorded respiratory rates are compared with those found in nembutalized dogs immersed in ice water.[21] In most experiments, the open-chest dogs did not exhibit any respiratory movements while the respirator was stopped during the perfusion. This phenomenon is attributed to depression of the respiratory center resulting from cerebral overoxygenation. In corroboration of this hypothesis, it was observed that blood from the vena

cava superior was materially lighter in color than the blood from the vena cava inferior and that the tongues of these animals remained light pink due to the presence of "arterialized" blood in the superficial veins of the heads.

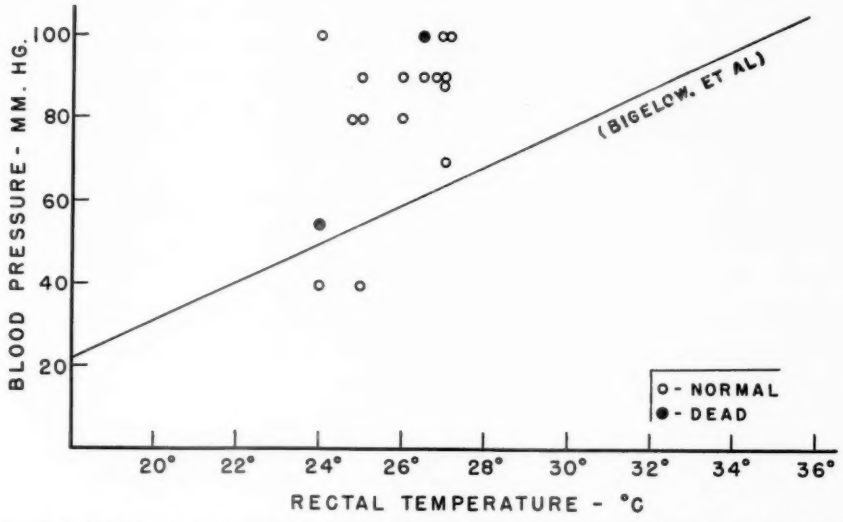

Fig. 5.—Carotid blood pressure during total by-pass of heart and lungs in hypothermic, open-chest dogs.

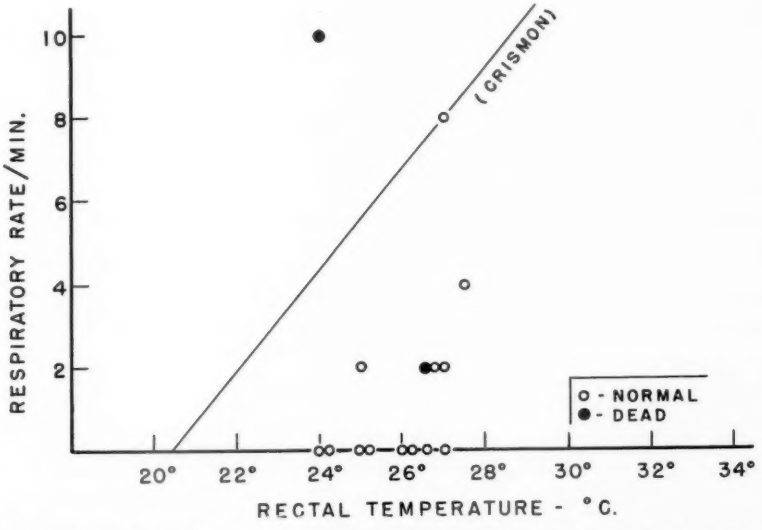

Fig. 6.—Respiratory rate during total by-pass of heart and lungs in hypothemic, open-chest dogs.

DISCUSSION

Although it has been shown that a gas dispersion pump-oxygenator can be used safely and efficiently for providing artificial circulation and oxygenation in closed-chest dogs, its application in open-chest animals has been limited, and its use in human intracardiac surgery prohibited, by the high mortality due to postoperative complications. The exclusive use of electrocautery in all surgical

procedures, as well as the described method of restoration of normal clotting time after the administration of large amounts of heparin, has permitted these difficulties to be overcome.

The delayed prolongation of clotting time after neutralization of the heparin effect by Protamine Sulfate has been observed previously.[6] The heparin-protamine titrations carried out during this period indicate that a larger amount of protamine is needed to reduce this delayed prolongation to normal. The explanation for this phenomenon is not clear at present. It seems, however, that the chemical conditions for a stable heparin-protamine complex are not present in the postoperative period. Studies[22] on the effect of pH have shown that alkalinity inhibits the heparin-protamine linkage, and it is possible that overventilation by the respirator during the postoperative period might have produced the same effect.

Since hemolysis is minimal, the drop in hematocrit and red cell count can be attributed to dilution of the donor blood by 5 per cent glucose in saline solution. We have gained the impression that the relatively high concentration of glucose is essential in the prevention of hemolysis. By comparing the percentages of reduction of various cell elements with the fall of erythrocytes, an estimation of the destruction of these cells during the procedure can be made. The destruction of the fragile platelets is marked, but a thrombopenic bleeding tendency after the experiment can be excluded since the transfusion of fresh blood raises the platelet count to higher levels.

The marked reduction of leukocytes during the perfusion is probably due to adherence of the white cells to the large surface of the extracorporeal circuit. The continuing drop of eosinophilic leukocytes is of interest and may be due to an effect upon the pituitary gland and/or the adrenal gland. Since we have not provided any evidence for such an assumption a speculative discussion of this point would be fruitless.

The constancy of the vitamin C blood level during the oxygenation by gas dispersion may indicate that the dog produces vitamin C at the same rate as it is destroyed. The high ascorbic-acid content of the blood after the transfusion eliminates the possibility of an acute vitamin C deficiency as a cause of a hemorrhagic diathesis.

The marked hypothermia induced by rapid cooling of the blood reduces the amount of blood necessary to be pumped and oxygenated by the instrument to the low cardiac output values found in hypothermia. This low blood flow can be reduced further by raising the blood pressure in the cerebral circulation so that only about one-fifth of the cardiac output requirement at normal body temperature is sufficient to supply the oxygen requirement of the brain and thereby prevent cerebral damage. The oxygen requirement of the rest of the body and of the heart, which is beating slowly and pumping coronary blood only, seems to be so low that the small amount of oxygenated blood pumped at low pressure is sufficient to preserve normal function of all organs.

SUMMARY

1. After the use of large amounts of heparin during the employment of a gas-dispersion-type pump-oxygenator, postoperative hemorrhagic manifestations

could be eliminated by the exclusive use of electrosurgical technique and the restoration of normal clotting time by a combination of Protamine Sulfate and fresh or decalcified blood.

2. Hematologic changes during the perfusion are due partly to dilution of blood with 5 per cent glucose in physiologic saline solution and partly to destruction and can be restored to normal by blood transfusions. The blood vitamin C level does not change during the oxygenation procedure.

3. By maintaining a high carotid blood pressure at 25° C. body temperature, as little as 30 to 40 c.c. of oxygenated blood per kilogram per minute is sufficient to cover the oxygen consumption of the body and to prevent anoxic brain damage in a one-hour by-pass of heart and lungs. Under these conditions consecutive survival of fifteen dogs has been achieved.

Acknowledgments.—We are greatly indebted to Mrs. Con Ball for statistical evaluation of the data and for criticism of the manuscript, to Mr. Raymond Jones for technical assistance, and to Dr. W. R. Kirtley, Ely Lilly & Company, Indianapolis, Ind., for Protamine Sulfate.

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A TECHNIQUE FOR THE PRODUCTION OF HYPOTHERMIA

Preliminary Report

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THE production and maintenance of a hypothermic state is potentially of great value in cardiac surgery. Because of the decreased metabolic needs of the tissues at lower temperatures, the heart can be excluded from the circulation for prolonged periods without producing irreversible brain damage.[1, 2] This permits clamping the venae cavae, opening the bloodless heart, and performing surgical procedures under direct vision. Such a technique lends itself well to the repair of septal defects and the correction of valvular abnormalities. Successful cases have already been reported in the literature.[3]

The methods used to lower body temperature have involved the application of cold to the skin surface or cooling of the inspired air. A prolonged period of exposure and deep anesthesia are usually necessary to overcome the heat-maintaining mechanism in a warm-blooded animal and to achieve a satisfactory hypothermic state (Fig. 1). This is an exhausting process and it leaves the animal in poor condition to withstand a major surgical procedure. Liver and cardiac muscle glycogen are decreased and a severe stress reaction occurs. In addition, once the defense mechanism has been overcome the temperature may continue to drop and rewarming is then difficult. This "overshooting" phenomenon has been the cause of many serious complications. Recent work by Laborit,[5] Huguenard,[4] and others[6] in France has indicated that certain antihistaminic drugs exert an inhibitory effect on the thermoregulatory center in warm-blooded animals. One of these compounds (Chlorpromazine) developed by Rhone-Poulenc of France has been made available to us for experimental use* and, after preliminary trials, the following technique has been evolved.

The subject, in the fasting state, is anesthetized with Pentothal Sodium and curare, and an endotracheal tube is inserted to maintain adequate pulmonary ventilation. The sensing bulb of a recording thermometer[7] is inserted into the rectum and a continuous record of body temperature is maintained.

The subject is placed in refrigeration blankets and an alcohol solution at 30° F. is circulated through the coils of the blanket (Fig. 3). Chlorpromazine is given in the dosage of 50 mg. intravenously and 100 mg. intramuscularly initially supplemented by 50 mg. intramuscularly every one to two hours dur-

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*Through the courtesy of Dr. Ernest Brown of Smith, Kline & French Laboratories, Philadelphia, Pa.

ing the period of hypothermia. No other medication is used and light anesthesia is maintained by Pentothal Sodium curare.

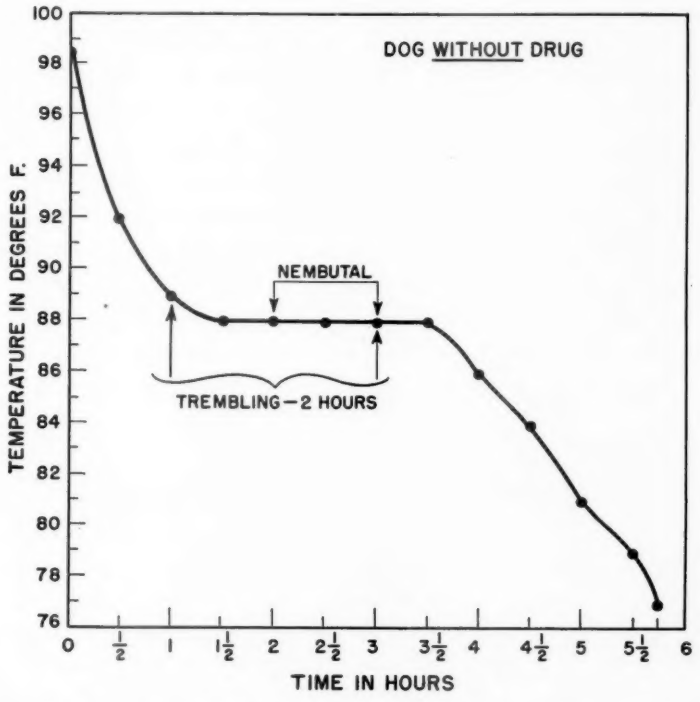
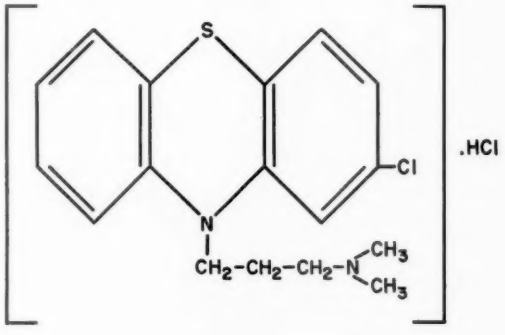


Fig. 1.—Temperature curve of dog refrigerated without Chlorpromazine. There is a prolonged period of shivering before the final drop of temperature occurs.



DIMETHYLAMINOPROPYL—N—CHLOROPHENOTHIAZINE HYDROCHLORIDE

Fig. 2.—Structural formula of Chlorpromazine.

When the body temperature reaches 80° F. the temperature of the refrigerant fluid is raised to 70° F. so as to maintain the hypothermic state at this level. All of the complications which we have encountered in the human being have occurred below 80° F., and, at the moment, we feel that this represents the limit of safety. Rewarming can be accomplished at any time by in-

jecting 50 mg. of Chlorpromazine intramuscularly and raising the fluid temperature of the blanket to 110° F.

RESULTS

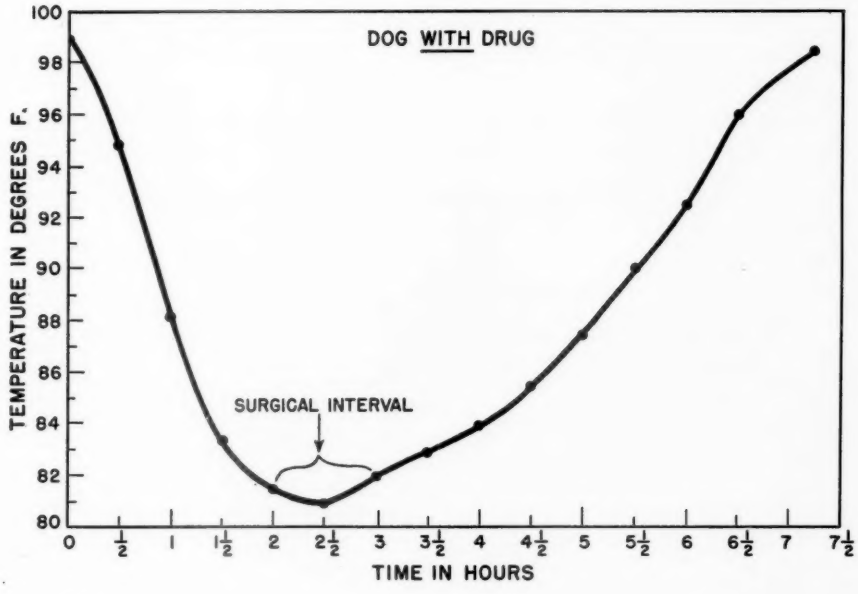
In the dog and in man, the body temperature begins to fall immediately and continues to drop in a smooth curve reaching 80° F. in fifteen to forty-five minutes. Shivering does not occur and there is no evidence of undue stress (Fig. 4). A minimal amount of anesthetic agent is required and thus the exhausting effect of prolonged deep anesthesia is avoided. If Chlorpromazine is given without the use of the refrigeration blanket, the temperature drops to from 92 to 94° F. and stabilizes at that level. Figs. 5 and 6 show a comparison of the effects of refrigeration with and without the drug in the dog and in man. It is apparent that with Chlorpromazine the temperature drops more rapidly and reaches a lower level with the same degree of refrigeration and anesthesia.

Fig. 3.—Refrigeration apparatus used in this experiment.

In the dog, the heart has been excluded from the circulation for periods up to fifteen minutes and the animals have recovered with no evidence of cerebral damage. The right atrium has been opened and interatrial septal defects have been created and repaired. Direct suture has been used for small defects, and a pedicle flap of the auricular appendage for large openings. This procedure has carried a 25 per cent mortality rate chiefly because of irreversible ventricular fibrillation. Because of this, it has been our feeling that

cardiac surgery under hypothermia should be attempted only in desperate cases of patients with no chance of survival without operation and in whom operation is not feasible without the help of this technique. Three patients have had exploratory cardiotomy, one adult for an intracardiac tumor visualized on angiocardiography which proved to be a thrombus at operation and

Fig. 4.



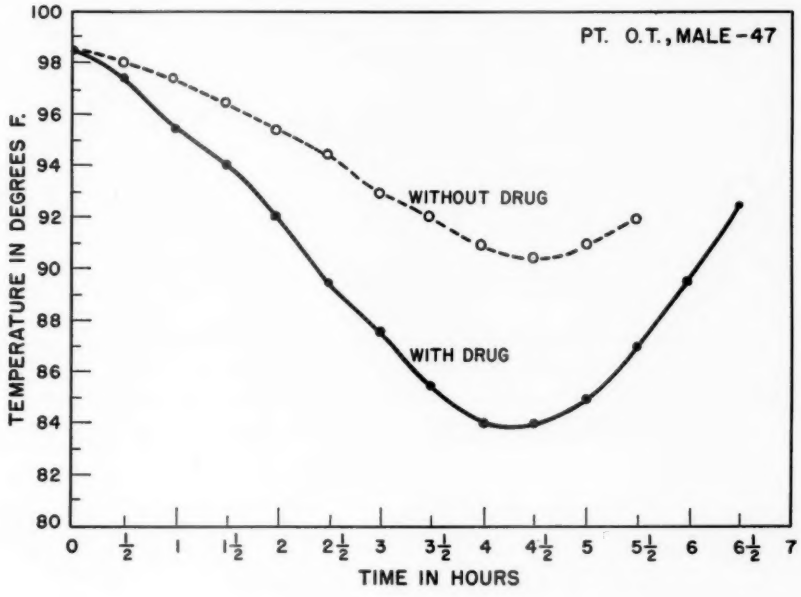


Fig. 5.

Fig. 4.—Temperature curve of dog refrigerated with Chlorpromazine. The smooth drop in temperature is obvious and there is no period of shivering.

Fig. 5.—Temperature curves in a patient refrigerated with and without Chlorpromazine. There is a more rapid drop to a lower temperature level with the drug.

two infants in terminal heart failure from septal defects. None survived operation, two developing ventricular fibrillation and one cardiac standstill.

In order to study the effects of hypothermia in the human being, seventeen patients have been subjected to artificial hibernation to control the hyperpyrexia in severe sepsis or to alleviate intractable pain due to inoperable carcinoma. All have recovered, but two developed cardiac irregularities (one, auricular fibrillation and one, ventricular extrasystoles) which reversed on rewarming. The other fifteen patients showed electrocardiographic changes related to decreased body temperature[8] but all reversed with no evidence of residual cardiac damage. It is noteworthy that in all patients developing significant arrhythmias the body temperature fell below the "safe level" of 80° F. Electroencephalographic studies revealed no abnormalities, and studies of renal function, liver function, and the circulating blood elements have shown no deleterious effects attributable to hypothermia.

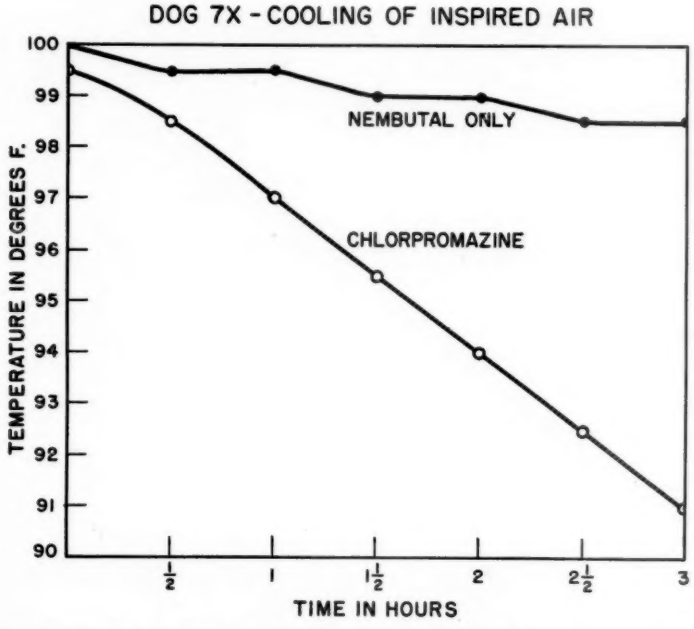


Fig. 6.—Temperature curves in a dog refrigerated by cooling the inspired air. With Chlorpromazine the temperature drops to a lower level.

The high incidence of cardiac complications is a limiting factor to the widespread use of the hypothermia technique in cardiac surgery at the present time. Further experimental work on the effect of cold on heart muscle and the mechanism of ventricular fibrillation is now being carried out in an attempt to obviate these complications. We feel, however, that this technique offers great possibilities for the future.

SUMMARY

1. A new technique for the production of a hypothermic state in the dog and in man has been described. This involves the use of refrigerated blankets

and a drug, Chlorpromazine, which exerts an inhibitory effect on the thermoregulatory center in mammals.

2. The only serious complication has been the high incidence of cardiac irregularities which have developed at low temperature levels (below 80° F.).

3. Hypothermia has a limited application at the present time and further experimental work is necessary to make this a safe procedure.

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CLINICAL USE OF LEVO-ARTERENOL DURING CYCLOPROPANE ANESTHESIA

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CARDIAC arrhythmias occur not infrequently with all the general anesthetic agents.[1, 2] In the presence of a heightened irritability of the myocardium occasioned by use of anesthetic drugs, small doses of epinephrine may cause such arrhythmias as premature beats, auriculoventricular block, slow ectopic rhythms, ventricular tachycardia, abnormal QRS complexes, and ventricular fibrillation.[3] These effects are more frequently noted in connection with the use of cyclopropane anesthesia.[4-6] For this reason most anesthesiologists prohibit the use of epinephrine during the administration of cyclopropane. Because of the structural similarity between epinephrine and levo-arterenol (l-norepinephrine) this interdiction has also been transferred to the latter drug.

In the course of our work in the treatment of shock with levo-arterenol,[7] forty-five patients were anesthetized with cyclopropane while receiving levo-arterenol by intravenous infusion. In none was there clinical evidence of toxicity.

Many of our patients were poor surgical risks in profound shock who had proved refractory to the usual blood- and fluid-replacement therapy and levo-arterenol was used to help treat the shock state. Without its use, a number of the operative procedures could not have been undertaken or would have had to be greatly curtailed. For these reasons, it was felt justified to try the supposedly dangerous combination of cyclopropane and levo-arterenol.

Clinical Material.—The clinical material on which we are reporting consisted of forty-five patients. Seven of these, in shock preoperatively, received levo-arterenol prior to and during the induction and maintenance of cyclopropane anesthesia. The operations involved consisted of:

1. Intra-abdominal procedures
   (a) Perforated viscus (two cases)
   (b) Intestinal obstruction (three cases)
   (c) Total gastrectomy for bleeding carcinoma (one case)
2. Urologic procedure
   (a) Suprapubic cystostomy for massive intravesical hemorrhage (one case).

Sponsored by the Veterans Administration and published with approval of Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect opinion or policy of Veterans Administration.

The levo-arterenol (l-norepinephrine) used in this study was supplied by the Department of Medical Research, Winthrop-Stearns, Inc., New York City.

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**Attending physician.

Thirty-eight other patients went into shock while undergoing operation and levo-arterenol therapy was initiated during the maintenance of cyclopropane anesthesia. The types of operative procedures included:

1. Intrathoracic procedures
   (a) Pneumonectomy (seven cases)
   (b) Lobectomy (four cases)
   (c) Repair of myocardial laceration (one case)
   (d) Thoracolumbar sympathectomy (ten cases)
2. Thoracoabdominal procedures
   (a) Splenorenal vein anastomosis (one case)
   (b) Esophagogastrectomy (one case)
   (c) Splenectomy (one case)
3. Intra-abdominal procedures
   (a) Abdominoperineal resection (two cases)
   (b) Colostomy (one case)
   (c) Revision of ileostomy (one case)
   (d) Resection of ileum for regional enteritis (one case)
   (e) Anterior resection for carcinoma of the sigmoid (one case)
   (f) Transverse colostomy for perforated rectum (one case)
4. Urologic procedures
   (a) Nephrectomy for carcinoma (three cases)
   (b) Nephrostomy for carcinoma of the bladder (one case)
   (c) Radical retropubic prostatectomy for carcinoma (one case)
5. Patient anesthetized but operation canceled because of persistent hypotension.

Administration of Levo-arterenol.—Levo-arterenol was administered by constant intravenous infusion, the rate (usually 1 to 3 c.c. per minute) depending on the adequacy of restoration of blood pressure. The concentration of the drug used was usually 8 μg per cubic centimeter. However, on rare occasions, concentrations as high as 16 μg per cubic centimeter were used.

Anesthetic Technique.—Twenty-three patients received cyclopropane with small amounts of ether and twenty-two received cyclopropane alone. Only small amounts of either anesthetic agent given infrequently were required by these patients, and depth of anesthesia was at no time judged to be below upper second plane. In all but three patients, anesthetics were administered via cuffed endotracheal tubes.

Results.—Continuous electrocardiographic observations were made in seven of the forty-five cases and at no time were changes of rhythm or contour noted. It is realized that cardiac arrhythmias which escape clinical detection may occur, but in none of our patients was there any clinical evidence of arrhythmia. No sudden deaths occurred. In twenty-three cases direct observation of the exposed heart disclosed no irregularity.

Nineteen patients had preoperative clinical and electrocardiographic evidence of moderate-to-severe myocardial disease. In several of these the surgical shock was so profound that hypoxia must have been present. After in-

stitution of levo-arterenol therapy, this group, like the others, did not show evidence of arrhythmia.

DISCUSSION

Of all the potent general anesthetics, cyclopropane appears to have the least deleterious effect on the peripheral circulation. Indeed, its central and peripheral circulatory effects are such as to be helpful in shock.[8-11] For this reason cyclopropane was chosen for these cases.

Since levo-arterenol became available for clinical use there has been hesitation in administering this pressor drug during cyclopropane anesthesia.[12] This hesitancy is based on experimental work done with laboratory animals. Garb and Chenoweth[6] used a dose of 30 μg per kilogram in a 2 c.c. volume administered as a single intravenous injection over a period of twenty seconds in cats deeply anesthetized with cyclopropane. They produced ventricular fibrillation with epinephrine in fourteen of twenty animals and with levo-arterenol in two of five cats.

Orth and associates,[5] in similar experiments on dogs, used single doses of 10 μg per kilogram in a 5 c.c. volume given intravenously over fifty seconds with deep cyclopropane anesthesia. They produced ventricular tachycardia in every one of twenty epinephrine-treated animals and in four of five levo-arterenol treated animals.

It should be noted that these doses are massive when compared to those we have used clinically. Our dosage of levo-arterenol usually ranges between 0.2 and 0.4 μg per kilogram per minute and rarely is higher while in Garb and Chenoweth's experiments the dose was 90 μg per kilogram per minute and in Orth's it was 12 μg per kilogram per minute. These represent 450 and 60 times, respectively, the dose we have used clinically. In addition, these laboratory experiments were carried out in deeply anesthetized animals.

Other workers, using the same laboratory animals, compared the effects of light and deep planes of cyclopropane anesthesia in the experimental production of ventricular fibrillation by epinephrine.[13, 14] They found that doses of intravenous epinephrine which produced ventricular fibrillation under deep anesthesia failed to do so during light cyclopropane anesthesia. It should be noted that all our patients were maintained in light planes of anesthesia.

There is one fully reported fatality in man from the combined use of epinephrine and cyclopropane.[4] This resulted from the injection of 2 c.c. of 1:1,000 epinephrine (2,000 μg) into four quadrants of the cervix for the purpose of producing an avascular field prior to a vaginal plastic operation. Waters[15] makes brief reference to a clinical case in which "accidental intravenous injection of 400 μg of epinephrine during cyclopropane anesthesia produced cardiac death." In another publication[16] he mentions one case in which intracardiac epinephrine during cyclopropane anesthesia caused death possibly due to ventricular fibrillation. The dose used in the latter case is not given. In these reported cases the amount of epinephrine used was of the order of magnitude injected experimentally to produce ventricular fibrillation.

It therefore seems reasonable to assume that these deaths resulted from the administration of unusually large doses of epinephrine during cyclopropane anesthesia.

It has been shown that the action of levo-arterenol is short lived and disappears within one to four minutes after termination of the infusion. For this reason, the appearance of arrhythmia would not seem to be as serious as with epinephrine, the cardiac effects of which may last as long as twenty-three minutes.[17, 18]

While the number of observations is small, we believe that the theoretical objections to the simultaneous use of levo-arterenol and cyclopropane, based on animal experiments and a few case reports, are not analogous to our clinical usage. When the combination of epinephrine and light cyclopropane anesthesia is used in animal experiments, arrhythmias are not produced. This more accurately reflects our clinical experience with cyclopropane and levo-arterenol. The combination appears to be safe and deserves further trial and study.

SUMMARY AND CONCLUSIONS

1. Forty-five patients in shock were given levo-arterenol by constant intravenous infusion during light cyclopropane anesthesia.

2. No untoward cardiocirculatory effects from this combination were noted. (Despite this, it is felt that the technique should be employed cautiously and discontinued in the event cardiac irregularities develop.)

3. The simultaneous administration of light cyclopropane anesthesia and a continuous intravenous infusion of dilute levo-arterenol does not appear to be as dangerous as hitherto believed.

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COMPLICATIONS FOLLOWING THE USE OF EFOCAINE

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DURING the past year and one-half, all reports reviewed in medical literature concerning the use of Efocaine have been favorable.[1-9] The drug has likewise been highly advertised by mail and at medical meetings. Comments such as the following have led to wider use of Efocaine: "Efocaine is a safe and effective local anesthetic that is indicated in the control of postoperative pain"[1]; "Local anesthesia with Efocaine may be advantageously used for intercostal nerve block as a means of postoperative pain control in upper abdominal surgery"[2]; "Efocaine, the aqueous, miscible, anesthetic agent is a safe, effective and highly desirable agent for the control of postoperative pain in ano-rectal surgery"[3]; "This drug is an effective means of pain control and is worthy of routine use in ano-rectal surgery"[6]; "Clinical study of this drug in more than 75 patients revealed that this agent was highly effective in the control of postoperative pain. There were no local or systemic toxic reactions; tissue sloughs or gross necrosis were not encountered."[7]

Judging from numerous inquiries I have received, many of the physicians who have not actually used Efocaine have read or heard about it. In our community, the public has been made aware by the newspapers and radio that a drug is now available which will render the postoperative period free of pain.

Despite the literature extolling Efocaine as a safe mixture, many isolated serious complications have arisen following its use. Evidently, these have not received wide enough attention, and not all have been reported. In view of all the favorable reports in the literature, physicians in whose practices these unfortunate problems have occurred may conclude that the complications were due to personal inexperience with the technique of regional analgesia employed and were not the fault of the drug. My associates and I might have reached the same conclusion except for the fact that in our institution in the past five years we have performed intercostal nerve blocks for surgical procedures and postoperative pain in over 2,000 patients, using one of the common local anesthetic agents, namely, Pontocaine (tetracaine) hydrochloride. Most of these patients had six or more intercostal nerves blocked at approximately the angles of the ribs. Our percentage of successful blocks in these patients is over 96 per cent.

Until we started to use Efocaine we did not encounter intercostal neuritis or paralysis following the blocks, although an occasional patient had tenderness at the site of the needle punctures. Of forty-one patients who received an intercostal Efocaine block for postoperative pain, the majority were free or partially relieved of pain and in eight instances the patients stated that they did not know

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where the incision was located. However, the first four patients in whom an intercostal block with Efocaine was performed, received 4 to 5 c.c. of the mixture, and three of these developed a severe intercostal neuritis.

When this occurred, we wrote Dr. R. W. Bartlett[10] since his experience with Efocaine in intercostal block was more extensive than ours. He answered that in their earlier cases he and his associates used 3 c.c. of Efocaine to each intercostal space but that this dose invariably caused local pain lasting up to four weeks. He also stated that with 1 to 1.5 c.c. doses of Efocaine he had gotten excellent relaxation and no instance of postoperative local pain. We then reduced our dose as recommended and never placed more than 2 c.c. of Efocaine under any one rib, yet in the next thirty-seven patients there still developed six severe cases of intercostal neuritis.

All of the nine patients with intercostal neuritis had identical reports. For the first two weeks following operation they were completely or relatively free of pain. They required little if any sedation. Most of them left the hospital in seven to ten days. After they had been home for from seven to ten days they noted pain which followed the course of one or all of the blocked intercostal nerves. The pain occurred not only at the site where the Efocaine was deposited, but radiated to the abdominal wall, and was characterized by burning which resembled a causalgia. The patients complained that contact with clothing or bed linen caused pain of a burning nature. This type of pain lasted for from two to six weeks before completely disappearing. Two of these patients consulted lawyers and intimated the possibility of legal action.

Because of our sizable previous experience with intercostal nerve blocks we did not believe our technique was faulty. However, our interest was stimulated, and from inquiries from colleagues at medical meetings we were able to find that we were not alone in having difficulties. Bonica[11] had six cases of postinjection neuritis in "over 100 cases." It is interesting to note that four of these cases of neuritis occurred in a series of twenty-five patients blocked intercostally for postoperative pain.[12] Eastwood[13] in a recent communication stated, "We have been using this drug and are beginning to have complications which may preclude its use on somatic nerves."

Four documented cases of transverse myelitis with varying degrees of severe paralysis were accumulated.[14-17]

Hubbard's[14] case occurred following a paravertebral lumbar sympathetic block with 3 c.c. of Efocaine at the level of the second lumbar vertebra. Three hours after the block the patient became partially paralyzed, retaining some motor power in her legs, mainly in the quadriceps and anterior tibials. Bladder control was lost but rectal control was retained. The patient's condition has not markedly improved in the last year.

Berg's[15] case followed a left decortication of the lung in which an intercostal block of the fifth, sixth, and seventh thoracic vertebrae for postoperative pain control was performed under direct vision using between 1 and 2 c.c. of Efocaine in each intercostal nerve, two to three inches from the intervertebral foramina. About six hours postoperatively, complete motor and sensory loss

from approximately the level of the eighth thoracic vertebra caudad was noted. Twenty days postoperatively there was no appreciable change in the patient's condition. The patient died approximately two months following the operation from tuberculosis without great change in his paralyzed condition at the time of death. Autopsy revealed an area of avascular myelomalacia at about the fifth thoracic vertebra in the spinal cord. The dura and the meninges showed no evidence of arachnoiditis. The cord above and below the fifth thoracic vertebra was normal, as was the cauda equina.

Griffith's[16] case occurred following repair of a diaphragmatic hernia by the transthoracic approach. The ninth rib was resected during the procedure. Three c.c. of Efocaine were injected under direct vision into the eighth, ninth, and tenth intercostal nerves just distal to the tubercle of the ribs. The left phrenic nerve was also injected with 1 c.c. of Efocaine. On the first postoperative day the patient began to complain of urinary difficulty. He was made to get up to stimulate the desire to void. On the second postoperative day the patient was up and about but could not urinate and required catheterization. On the third postoperative day the patient complained of not being able to move his legs. Physical examination revealed (1) sensory loss below the level of the eighth thoracic vertebra, (2) complete motor paralysis of the left leg with positive Babinski reflex, and (3) almost complete motor loss of the right leg, but the patient could still weakly extend and flex toes on the right and the Babinski reflex was negative. The Efocaine was injected Nov. 10, 1952, and I saw the patient Dec. 13, 1952. At that time, Dr. Griffith demonstrated the fact that the patient was showing very slow improvement with return of sensation and partial return of the motor function of both legs. The patient is able to elevate slightly both legs, the right leg better than the left, but there is still a marked weakness and hypotonia of all muscles of the legs. Cystometrograms made Nov. 21, 1952, were consistent with atonic bladder. On repetition, Nov. 28, 1952, there was some evidence of improvement, and the patient had a desire to void when 400 c.c. were present in the bladder. Dr. Griffith feels that improvement will continue, but the prognosis for complete recovery is very poor.

During a discussion of Efocaine on a recent visit to Minneapolis, Dr. Knight and Dr. Luth[17] told me of a case of transverse myelitis following the use of Efocaine. The patient had been operated upon for a lesion which turned out to be a small tuberculoma of the lung. The fourth rib was resected during the operation. At the completion of the resection of the lesion 2 c.c. of Efocaine were injected intraneurally at the transverse processes of the second, third, fourth, fifth, and sixth thoracic vertebrae. On first postoperative day the patient exhibited the signs and symptoms of a transverse myelitis. The lesion was judged to be at the level of the sixth thoracic dermatome. It has been approximately two months since the injection, and the patient is showing some return of motion in the quadriceps and tibial group of muscles.

At first, it was difficult for us to understand how a solution placed two to three inches away from the spinal cord could cause a transverse myelitis. Dr. Ward[18] and Dr. Johnson,[19] Professor of Neurosurgery and Professor of Anatomy, respectively, at the University of Washington, were consulted, and

they emphasized the fact that the perineural spaces of any peripheral nerve, while essentially filled with loose areolar tissue and so forth, are still continuous with those of their roots at least as far centrally as the spinal cord (Figs. 1 and 2). Dr. Ward[18] elucidated the subject by saying that if an adequate quantity of India ink is injected intraneurally into the sciatic nerve at the sciatic notch,

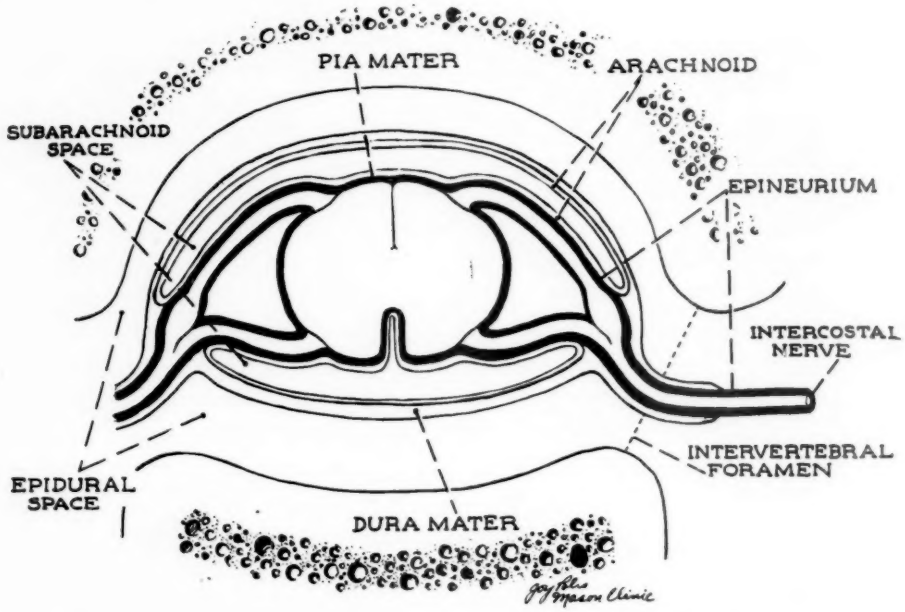

Fig. 1.—Cross section of the spinal cord. Note that the epineurium of the nerve is a continuation of the pia mater. This essentially makes a pathway for fluid injected intraneurally to undergo retrograde diffusion and reach the spinal cord.

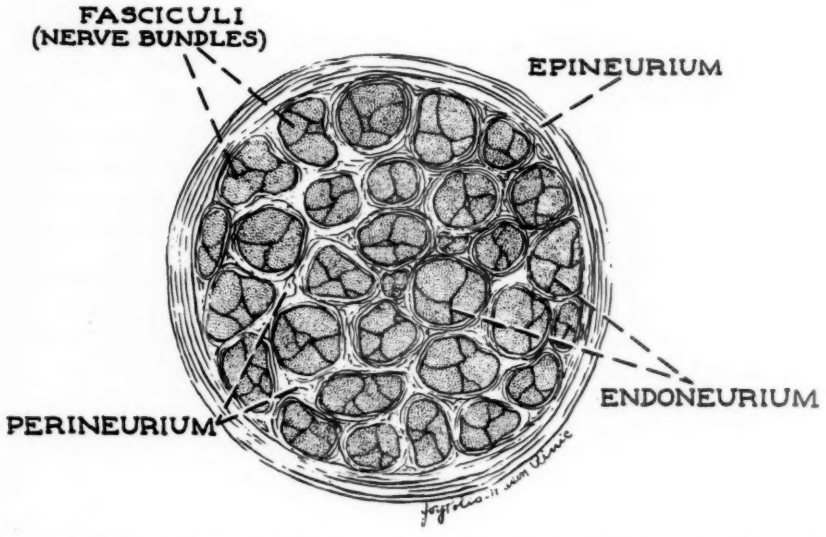

Fig. 2.—Cross section of an intercostal nerve. Note that while the interstices between the nerve bundles (fasciculi) are filled with connective tissue called perineurium, they are potential avenues for retrograde diffusion of materials injected intraneurally.

the ink can be found in the subarachnoid space from minutes to hours later. This retrograde diffusion could be the explanation of the transverse myelitis which has occurred with Efocaine.

In addition to transverse myelitis and intercostal neuritis from Efocaine, cellulitis and sloughs have been noted, although to date I have not seen any. However, Hubbard[14] has seen severe cellulitis following block of the facial nerve with 2 c.c. of Efocaine, block of the coccygeal nerves bilaterally with 2 c.c. of Efocaine on each nerve, block of the perirectal area with 4 c.c. of Efocaine, and bilateral block of the perineum with 3 c.c. of Efocaine on each side. The signs and symptoms of cellulitis lasted from seven to ten days in these cases. Dr. Knight and Dr. Luth[17] also told me of a slough of the tissue around the anus. This occurred in a doctor, following the injection of 1 c.c. of Efocaine on each side of the rectum to relieve postoperative pain of a hemorrhoidectomy. The slough necessitated additional hospitalization of approximately five weeks. Spano[20] has had three cases of ischiorectal abscesses following the injection of Efocaine into the rectal sphincter to relieve the postoperative pain of a hemorrhoidectomy.

The exact cause of these reactions where Efocaine has been used is to date not solved. Efocaine is a mixture composed of "1 per cent Procaine and 0.25 per cent Procaine hydrochloride as the anesthetic base, 5 per cent butyl-p-amino-benzoate, 2 per cent polyethylene glycol-300, and 78 per cent propylene glycol as the aqueous-miscible solvent, and 0.1 per cent sodium metabisulfate and 1:2,500 phenyl mercuric borate as the preservatives."[21] Weinberg[22] states, "The subcutaneous, intramuscular and perineural injection of Efocaine produces no significant permanent damage to the tissue involved and is the same order as that seen following the injection of procaine or penicillin-in-oil. The injection of Efocaine does not result in a foreign body giant cell reaction. There is no apparent permanent storage of Efocaine at the site of injection."

It must be pointed out that Weinberg's experiments were conducted using rabbits, guinea pigs, and rats, and the tissue reactions may not be identical with those in man. He attributed the focal degeneration of the myelin sheath in injected brachial plexuses of rabbits as being caused by the injection of a large volume of the drug rather than by the drug itself. Perhaps in view of the side results of Efocaine in the human being, this should be reinvestigated. It is interesting to note in our patients with neuritis that the neuritis did not occur until a period of two weeks elapsed, and then its characteristics resembled those which are often seen when a peripheral nerve is regenerating.

SUMMARY

Cases of neuritis, transverse myelitis, cellulitis, tissue slough, and abscess following the use of Efocaine are cited.

How Efocaine injected paravertebrally and intercostally can result in transverse myelitis has been proposed.

CONCLUSIONS

Some of the complications observed may only be coincidental with the use of Efocaine rather than be caused by the mixture itself, but nevertheless they

have occurred often enough so that Efocaine as the responsible factor cannot be disregarded. Perhaps before injecting Efocaine it is best to consider this question: When a drug or mixture is capable of producing transverse myelitis, intercostal neuritis, or a tissue slough, should it be used routinely in patients whose pain is only temporary in nature, for example, postoperative pain, and in whom surgery for a curable disease such as diaphragmatic hernia is being performed?

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THORACIC NEURENTERIC CYST

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RECENTLY a large retropleural thoracic cyst resulting from persistence of an accessory neurenteric canal was encountered in a child who complained of persistent cough and wheezing. Because of its rarity, embryologic interest, and suitability for satisfactory surgical treatment if properly recognized, its diagnostic, pathologic, and therapeutic features seemed worthy of description.

CASE REPORT

P. P. (A379247), a 4½-year-old boy, entered the Children's Medical Center Nov. 2, 1951, because of severe cough and wheezing respirations of nine months' duration. His father complained that because of the wheezing it was impossible for anyone to sleep in the same room with him. He remained afebrile and the cough was productive only rarely of small amounts of mucus. However, one week prior to admission he did cough up two teaspoonsful of bright blood following a prolonged paroxysm.

Family history was not contributory and the delivery was uneventful. He had whooping cough as an infant. Mental development was commensurate with the other eleven children of the family, although he was somewhat small for his age.

Physical examination revealed a pale underdeveloped boy who was dyspneic and obviously in acute respiratory distress. Temperature was 101° and pulse 100. The trachea was deviated to the left. His neck was short, suggesting a Klippel-Feil syndrome, and there was mild kyphoscoliosis most pronounced at the third dorsal vertebra. There was no irregularity of the overlying skin in this area. Respiratory excursions were labored but equal bilaterally and there was no sternal retraction. Coarse rales were audible over both lung fields. Neurological examination elicited no motor, sensory, or reflex abnormalities. The patient had normal rectal and bladder sphincter control.

Roentgenologic examination revealed multiple congenital anomalies of the spine extending from the fifth cervical vertebra to the fifth dorsal vertebra characterized by unmatched hemivertebrae and spina bifida. The vertebral bodies of the first dorsal vertebra through the fourth dorsal vertebra appeared fused. In the region of the third dorsal vertebra there was an anterior circular defect measuring 1.6 cm. in diameter (Fig. 1). A soft tissue mass in the superior-posterior mediastinum projected toward the right and produced forward displacement of the trachea.

Myelography showed deflection but no obstruction to the passage of the opaque medium in this region and none of it entered the extraspinal mass. It was concluded that the lesion was an anterior meningocele which protruded through the large vertebral defect into the right hemithorax and that the neck of the sac had probably become sealed off from the subarachnoid space.

On Nov. 9, 1951, laminectomy was performed at the third and fourth dorsal vertebrae (by D. D. M.). The spinal canal was markedly widened in the area of the spina bifida. The dorsal dura was intact and normal in appearance but almost twice normal width. It was opened revealing a normal-appearing spinal cord except for atrophy of nerve roots on the right. After dividing the dentate ligaments and two or three of the atrophic dorsal rootlets, the cord was rotated to expose a stalk approximately 5 to 6 mm. in diameter which

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emerged from the middle of the anterior surface of the cord and passed through a circular defect in the anterior dura and vertebral body. The stalk was solid and appeared to be fibrous tissue which merged intimately with the ventral surface of the cord. Adhesions to the stalk were divided, following which it was doubly ligated with silk and divided. A patch, 1.5 by 1.5 cm., of the redundant dorsal dura was used as a free graft to close the defect in the anterior dura, and routine closure of the rest of the wound carried out. Convalescence was uneventful and the patient was discharged on Dec. 2, 1951.

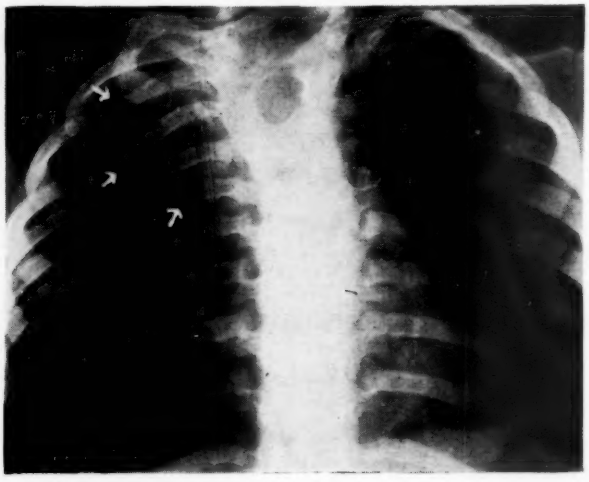
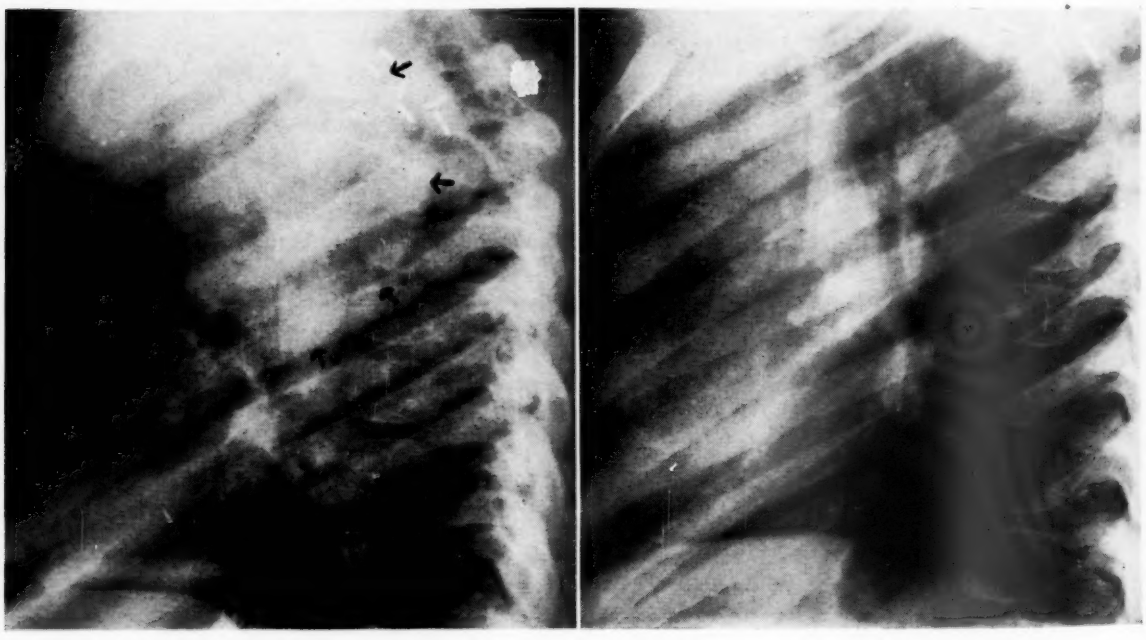


Fig. 1.—Anteroposterior chest roentgenogram which reveals a mass at the right apex (outlined by arrows). Note multiple anomalies of vertebral bodies fifth cervical through fourth dorsal vertebrae and the 1.6 cm. defect which was traversed by a stalk extending from the neurenteric cyst to the anterior spinal cord surface.



A. *B.*

Fig. 2.—*A*, Lateral chest roentgenogram prior to thoracotomy showing forward tracheal displacement produced by the large intrathoracic mass.

B, The same view five months after thoracotomy illustrating return of trachea to normal position.

Symptoms of tracheal compression persisted and roentgen examination revealed no significant decrease in size of the intrathoracic mass (Fig. 2, *A*). Therefore, the patient was readmitted to the hospital and thoracotomy was performed on Feb. 1, 1952 (by G. W. H.). The pleural cavity was entered through the right fourth intercostal space cutting the fifth and fourth ribs posteriorly. A smooth rounded mass which occupied the posterior apical portion of the right hemithorax (Fig. 3) was easily seen. Following division of the azygos vein the pleura was incised and the cystic mass exposed. Palpation indicated that this was probably not a meningocele because it had a very thick wall. Viscid mucoid material, which bore no resemblance to spinal fluid, was aspirated. The cyst wall measured from 0.5 to 1.0 cm. in thickness, and its lining resembled intestinal mucosa suggesting the possibility that this was an esophageal duplication. Dissection of the mass was accomplished except for its posterior attachments to the vertebral bodies and ribs. Following excision of the redundant cyst wall, the resultant small cavity was obliterated by folding in the remaining tissue with three layers of silk. The dural graft previously placed over the circular vertebral defect was intact. Pleura was approximated and the chest was closed without drainage. The postoperative course was uncomplicated and symptoms of tracheal compression disappeared entirely (Fig. 2, *B*). Eleven months later the patient continues to be symptom free.

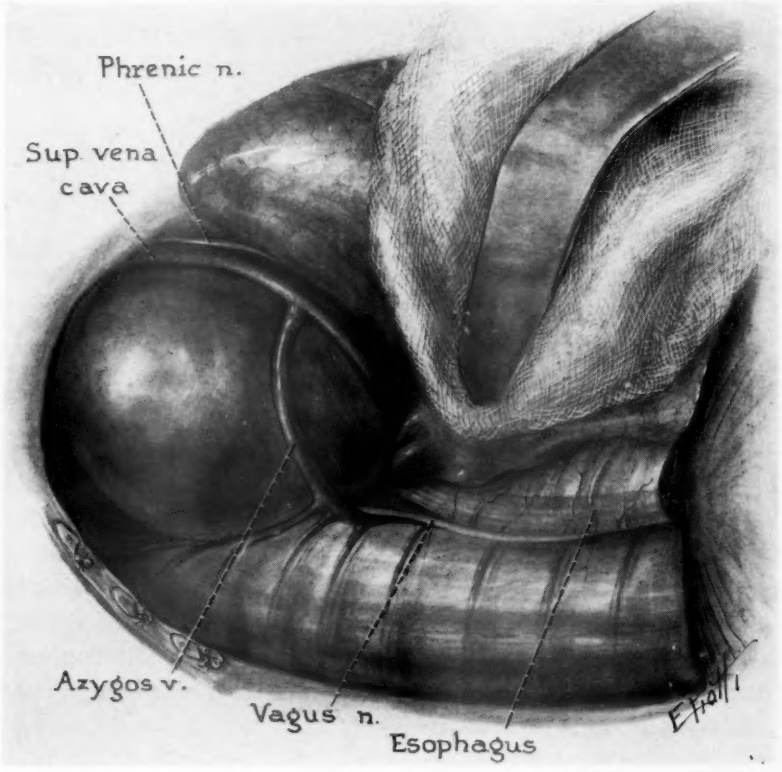


Fig. 3.—Appearance of the retropleural mass at operation.

The cyst wall showed no evidence of inflammation. Microscopically the mucosa varied from pseudostratified columnar epithelium to a single layer of cuboidal cells. Deep to a loose submucosa were two thick layers of interwoven muscle fibers. Nerve bundles and blood vessels were scattered throughout the muscle fibers.

It would be impossible to distinguish this lesion from a duplication of the esophagus by microscopic examination. Grossly, however, there were two important features which

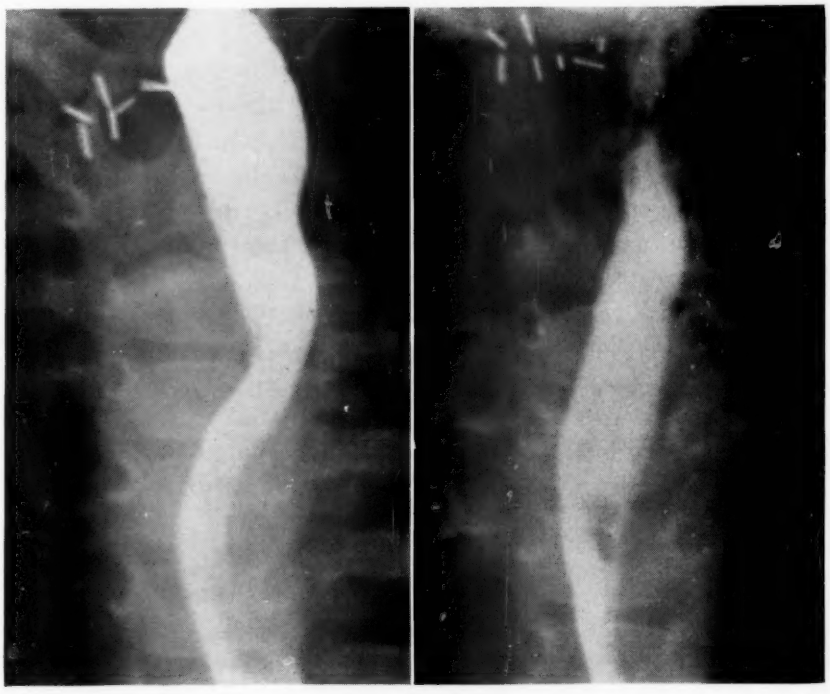
suggested another origin: (1) a duplication is usually intimately fused with the esophageal muscle layer whereas this anomaly had no such relationship; (2) the presence of a fistulous tract extending from the cyst through the vertebral defect and dura to the anterior surface of the cord strongly suggested that the etiology was related to an accessory neurenteric canal.

EMBRYOLOGY

Early in the development of the human embryo there is a small connection between the yolk sac and surface of the embryo called the neurenteric canal. This fistulous structure traverses the primitive knot and connects the future enteric cavity with the neural groove in the region of the coccyx. Bremer[1] drew a distinction between this short lasting neurenteric canal and any patent or solid tract which might occur between the alimentary tract and the dorsal midline structures cephalad to the coccygeal tip. He stated that the latter condition represents an ectopic or accessory neurenteric canal because the primitive knot is not traversed. He cited the experimental work of Lereboullet,[1] who, in 1868, following artificial insemination of pike embryos, noticed that some specimens had longitudinal clefts extending between normal heads and normal tails thus exposing the yolk-sac surfaces. By delaying fertilization until frog ova were overripe, Hertwig,[2] in 1892, was able to produce similar conditions. These experimentally produced open clefts have all characteristics of the minute human neurenteric canal but differ from it in the large size and more cephalad location of the former. Bremer[1] referred to reports in the literature of three stillborn infants each with wide-open clefts between the spinal cord and different portions of the alimentary tract (pharynx, esophagus, stomach, and intestine) which provided direct communication from the lumen of these structures to the dorsal cutaneous surfaces.

Just as it is possible to find vitelline-duct remnants varying from a patent tube connecting the ileum and umbilicus, to a cyst in the center with a patent tract either to the skin or to the ileum, or to a solid fibrous band, and most often there is no remnant at all, so will the dorsal neurenteric fistula occasionally persist in one of these many forms. The outstanding difference is that while the vitelline duct traverses a cavity, no evidence of its former presence can be found after it disappears. The neurenteric fistula, on the other hand, passes through all the dorsal midline structures and usually leaves some permanent evidence of its former presence such as: (1) a widened vertebral body resulting from bony proliferation in an attempt to fill the gap following disappearance of the tract; (2) a circular defect in the body of a vertebra produced by persistence of a tract which forces bone to form around it; (3) a bony or cartilaginous spur which projects into the spinal canal delaying union of the vertebral halves to the extent that independent pedicular processes form. When these finally do unite, following disappearance of the dorsal fistula at a time later than normal, the pedicular processes fuse to form a median spur. This condition is known as diastematomyelia. Recalling its embryologic origin, it is possible that the entire neurenteric sinus might persist rather than only a segement as occurred in this case. Keen and Coplin[3] reported such a lesion, in 1906, which was found in the sacral region of a 2-year-old girl. This tube

measured 4 to 5 mm. in diameter and extended from the dorsal rectal wall through a sacral vertebral defect and the nerve roots of the cauda equina to the skin.



A. *B.*

Fig. 4.—*A*, Anteroposterior roentgenogram of barium-filled upper esophagus indicating deviation to left produced by the expanding retropleural neurenteric cyst. Note the normal esophageal indentation on the left side below this level produced by the aortic arch.

B, Roentgenogram five months following operation illustrating normal position of the esophagus.

SYMPTOMATOLOGY

Symptoms produced by such an anomaly naturally will depend upon the anatomic location of the persisting embryologic tract. In this case, there was no esophageal or cutaneous connection and the spinal cord itself was not actually malformed although the stalk did merge into its anterior surface. The expanding cyst produced tracheal compression which resulted in severe cough accompanied by a loud, wheezing type of respiration. There was not sufficient obstruction of the esophagus to interfere with deglutition. Had the fetal type of pseudostratified epithelium progressed to form gastric mucosa, a severe inflammatory process might have resulted from secretion of hydrochloric acid and pepsin. Mucosal ulceration with inflammation spreading to the surrounding structures could produce marked irritation and symptoms even in the absence of a large expanding mass. Perforation into the pleural cavity, the trachea, or the esophagus with disastrous results might follow such an intense chemical reaction. A simple fistula from the esophagus to the back would allow liquids to flow out the external orifice and would call attention

to the abnormality early in life. Meningitis might appear any time after birth if such an esophageal fistula terminated in the subarachnoid space.

ROENTGEN EXAMINATION

Roentgen examination of such a patient usually will be informative but not always diagnostic. In this case, the circular defect in the body of the third dorsal vertebra, associated with a mass projecting into the right thoracic cavity, suggested the presence of an anterior meningocele. Barium swallow indicated displacement of the esophagus to the opposite side although the obstruction was not sufficient to produce symptoms (Fig. 4). A tracheogram did not seem indicated because it was obvious from the symptoms and the location of the lesion that this structure was being compressed (Fig. 2). Myelogram revealed widening of the neural canal in the cervical and upper dorsal regions. No dye passed anteriorly into the cyst. The dye distributed itself around this defect in such a manner as to outline quite sharply its circumscribed margin, all of which suggested that there was some connection between the anterior mass and the subarachnoid space although not necessarily a patent one. There does not appear to be any method by which this lesion could positively be differentiated from an anterior meningocele on roentgen examination.

TREATMENT

Persistence of any portion of a dorsal intestinal fistula (accessory neurenteric canal) should be treated by surgical excision as soon as symptoms call attention to its presence. It may be impossible to remove the outer cyst wall entirely because of adhesion to other structures although this is certainly desirable. In such instances it is permissible to excise the redundant portion and fold the remaining wall in to obliterate the cavity. However, if aspiration reveals the cyst contents to be acid or bloody, the importance of completely excising the lesion or of stripping away any remaining mucous membrane cannot be overemphasized. When a stalk penetrates the spinal canal, dura, and subarachnoid space, meticulous care must be taken to close the meningeal defect either directly or by grafting or approximation of the overlying soft tissues. This obviously implies division of any connections with the spinal cord itself. Great care should be exercised to manipulate the spinal cord as little as possible and to avoid injury to any intraspinal structure which might contain functioning neural tissue.

SUMMARY

The case of a 4½-year-old boy complaining of repeated upper respiratory infections, persistent cough, and loud wheezing is described. Examination revealed multiple spinal anomalies including a circular defect of the vertebral body of the third dorsal vertebra associated with a right intrathoracic mass. This was incorrectly diagnosed preoperatively as an anterior meningocele. Laminectomy was first performed, a fibrous stalk attached to the anterior-cord surface was severed, and the anterior dural defect was closed. Thoracotomy with subtotal excision of the retropleural cyst wall and complete obliteration of

the remaining cyst cavity was performed three months later. Microscopic examination of the specimen revealed fetal intestinal epithelium and layers of smooth muscle which resembled duplication of the esophagus. We are indebted to Bremer[1] who clarified the embryologic origin of this interesting lesion. He stated that it is a cyst of neurenteric origin which retained its dorsal spinal connection but lost both remaining distal segments (esophageal and cutaneous). The patient had a successful recovery and remains symptom free.

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Editorial

Dangers of Conservative Surgery in Abdominal Emergencies*

IN THE era before antibiotics, modern anesthesia, and the blood bank, many surgeons were fearful of performing extensive and definitive operations on patients who were desperately ill as a result of abdominal catastrophes. Shock was interpreted as a contraindication to surgical intervention, localized peritonitis was considered a reason for avoiding exploration, and the philosophy of the surgeon was to do as little as possible and to hope for the best.

Developments in surgical technique, in anesthesia, and in the physician's ability to control hypotension and infection have resulted in a reversal of the age-old policy of conservative treatment in certain types of desperately ill patients. It is now being recognized that a definitive operation, although extensive and perhaps prolonged, is safer than a smaller operation which does not accomplish its purpose. Surgeons now realize that it is not the operation which causes the death of critically ill patients but the disease for which the operation is being performed. If the operation does not correct the pathology, the patient is doomed and might as well have had no operation at all.

Several examples of this new type of thinking can be found in the field of abdominal surgery. For many years surgeons have believed that a loop ileostomy was the safest treatment for a patient with fulminating or acutely toxic ulcerative colitis. They disregarded the fact that the ileostomy did not remove the source of the toxicity, that the danger of perforation was not removed, and that the patients still could bleed to death or lose enormous quantities of protein from defunctionalized colons. Fear that the friable bowel might be perforated during its removal and that fatal peritonitis might ensue prevented them from performing ileostomy and simultaneous colectomy. Today we recognize that the mortality rate of operations for acute toxic ulcerative colitis is lower if the colon is removed and the disease eradicated. Since the discovery of the antibiotics, we have lost our fear of contamination peritonitis and no longer view a perforation of the colon at operation as an irrevocable tragedy. A leak that continuously pours the contents of the bowel into the peritoneal cavity, as may happen after ileostomy, is still as fatal as ever, but contamination, if followed by an adequate peritoneal toilet, is likely to be of little consequence.

Perforations of the colon, such as occasionally occur with carcinoma or diverticulitis, are sometimes managed by inadequate operations which fail to deal directly and completely with the perforation itself. In the past, it was considered good practice to treat a patient with a free perforation of the

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sigmoid by transverse colostomy. This diversion of the fecal stream was supposed to limit the amount of contamination and result in a localization of the peritonitis. Surgeons were afraid to attack the cause of the peritonitis directly for fear of spreading the infection. Today, with the protection afforded by antibiotics, there is little excuse for such half-hearted measures, even in patients who are desperately ill. It appears that a direct attack on the source of the contamination, with exteriorization or resection of the involved segment, drainage of abscesses, and aspiration of as much as possible of the pus and feces in the peritoneal cavity, affords the patient the best chance of survival.

The wheel of surgical practice threatens to make a complete turn toward the days when surgeons eviscerated patients with peritonitis and lavaged their intestines in antiseptic solutions. Valueless as the antiseptics have proved, nevertheless a thorough peritoneal lavage with removal of as much pus and foreign material as possible is today practicable and worth while. Any contamination of clean parts of the cavity can be controlled by antibiotic therapy. Most important is the elimination of the source of contamination. If this is done, the patient has a better chance of recovery than he does following a small operation which diverts the fecal stream but leaves a leaking column of stool below the colostomy.

The same principles apply to the treatment of acute gastroduodenal hemorrhage and other abdominal emergencies. The surgeon, the anesthetist, and the blood bank should be prepared not to sustain the patient for a minimum procedure but to support him during a definitive operation. It is the disease, not the operation, that causes death, and the first responsibility of the surgeon is to eradicate the disease.

—George Crile, Jr.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

TREATMENT OF TUMORS OF THE PAROTID SALIVARY GLAND

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NEW YORK, N. Y.

(From the Pack Medical Group)

INTRODUCTION

THE inadequacy of past methods of treating parotid tumors has produced a high rate of recurrences and treatment failures, which has resulted in confusion concerning the natural history of parotid neoplasms. Many physicians believed that parotid tumors originated from multicentric foci, and they attributed the high recurrence rate to the concept that new tumors developed after the treated ones had been cured. Another empiric and fallacious practice was that advanced by McFarland, who believed that the recurrence rate was lower when the larger parotid tumors were excised; therefore, he advocated the practice of watchful waiting until the tumor became "ripe" before excising it.[27, 28]

It has been determined that most tumors arise as a single nidus and gradually grow to infiltrate the glandular parenchyma and sometimes to compress or infiltrate the facial nerve. The high recurrence rate is the result of inadequate removal because of fear of damaging the nerve. After a period of growth, malignant parotid tumors will invade contiguous cervical tissues, infiltrate into the pterygomandibular space, produce metastases to regional lymph nodes, or disseminate by way of the blood stream to distant organs.

The purpose of this review is to present criteria for treating parotid neoplasms and to describe surgical techniques which will permit their resection without damaging the facial nerve unless the nerve has been invaded by cancer, in which case it is sacrificed. The technique to be described has been utilized in a large number of patients with gratifying results. Histologic features and nosology of parotid neoplasms have been adequately described and will not be labored in this review.[20, 31, 42] One hundred patients with parotid tumors treated at the Pack Medical Group are analyzed to glean an insight into those factors by which an early diagnosis can be established, the type of anatomic structure determined, and the results of the therapy analyzed.

CLASSIFICATION OF PAROTID TUMORS

For determining the type and extent of treatment for different parotid neoplasms the simplest and most adequate classification into which the majority fit is arrived at by merely subdividing the group into (1) benign epithelial tumors (mixed tumors are the most frequent), (2) malignant epithelial

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tumors (carcinoma), and (3) miscellaneous, which includes a heterogeneous group comprised of other than epithelial elements.

Complete classifications have been presented recently by Rawson and associates,[42] Kirklin and co-workers,[20] Marshall and Miles,[31] and Stein and Geschickter.[47] Such a complete classification is of importance in understanding the pathologic development of the salivary gland cellular elements and in determining the radiosensitivity of certain tumors, and is of prognostic value.

CLASSIFICATION OF PAROTID TUMORS*

A. Benign epithelial tumors
   1. Mixed tumor
   2. Papillary cystadenoma lymphomatosum (Wharton's tumor)
   3. Sebaceous gland tumor
   4. Adenoma
      a. Ordinary adenoma
      b. Oncocytic adenoma

B. Malignant epithelial tumors
   1. Cylindroma
   2. Malignant papillary cystadenoma
   3. Adenocarcinoma
   4. Squamous-cell carcinoma
   5. Undifferentiated carcinoma
   6. Mixed carcinoma (mucoepidermoid carcinoma)

C. Miscellaneous tumors
   1. Benign
      a. Cysts
      b. Lipoma
      c. Neurofibroma
      d. Lymphocytic tumor
      e. Hemangioendothelioma
   2. Malignant
      a. Neurosarcoma
      b. Fibrosarcoma
      c. Melanoma
      d. Lymphosarcoma
      e. Hodgkin's disease

It is difficult at times to establish the exact pathologic type because salivary gland tumors may develop rather bizarre formations or combinations to preclude a clear-cut classification of type. Not infrequently, an apparently benign tumor will show infiltration of the capsule while others will have one locus which is malignant and will produce distant blood-borne metastases. Such unusual behavior of parotid neoplasms makes essential a complete understanding of the natural history of this oncologic entity in order that proper criteria for therapy be established and exact techniques developed.

CLINICAL FEATURES

Incidence.—There have been approximately 20,000 patients with tumors observed at the Pack Medical Group of which 100 were of the parotid gland.

*After Rawson, Howard, Royster, and Horn.[42]

Thus, parotid neoplasms represent 0.5 per cent of all neoplasms. Hellwig[15] described an incidence of 2 per cent of 4,352 tumors at Wichita, Kan. Schreiner and Mattick[44] noted an incidence of salivary tumors of 1 per cent at the State Institute for Maligant Diseases at Buffalo, N. Y. Its rarity is stressed by McFarland,[27] who collected only 310 mixed tumors in the course of twenty-five years in Philadelphia. Ahlbom[1] observed only 254 tumors of the salivary gland during twenty years at the Radiumhemmet, which institute treats patients with neoplasms from the entire country of Sweden.

It is difficult to compare the true incidence in relationship to other neoplasms since certain treatment centers have disproportionate numbers of patients bearing parotid tumors referred to them. These larger series treated by certain standard regimes have become available for comparative purposes and supply data for understanding the natural history and methods of treatment of parotid neoplasms.

Etiology.—There is no definite factor or group of factors in this series which could account for the production of these tumors. Analysis of the data does not reveal any correlation between such factors as poor oral hygiene, previous infection, associated diseases such as syphilis or tuberculosis, or repeated trauma to account for the development of the neoplasm.

Age.—In this series the average age of the 100 patients with tumors of the parotid gland was 45.2 years. The average age for patients with benign tumors was 36.1 years, the youngest patient was 7.5 years old, and the oldest was 62 years old. In the 44 patients with carcinoma of the parotid gland the average age was 52.9 years, the youngest being 15 years and the oldest 78 years of age. It is of interest that a malignant parotid tumor was observed in a newborn infant,[29] and Duthoit[11] described one in a child 6 weeks of age. Wood[51] described a tumor of the parotid in a child 7 months old. The peak incidence for patients with benign tumors is less than that for patients with carcinoma.[42] There is so much overlapping, however, in the ages of the two groups that the age of a given patient cannot be utilized to determine if the given tumor be benign or malignant.

Sex.—Of the 100 patients with parotid tumors, 56 were men and 44 were women. The sex distribution of patients with benign tumors was similar for the two types: 28 patients were men and 26 were women. Men bore cancer somewhat more frequently than women. Of the 46 patients with parotid cancer, 28 were men and 18 were women.

Symptoms.—The constant history related to the presence of a slowly growing, painless mass in the vicinity of either ear. The mass continued to grow in size over a period of years, and the majority of patients presented themselves because of cosmetic disfigurement.

Five patients, on admission, presented evidence of facial nerve paralysis. In each case the histologic examination of the tumor revealed carcinoma, and in all instances the patients died of the cancer.

An asymptomatic mass was uniformly the symptom of patients with benign tumors, while in patients bearing carcinoma, in addition to the mass, some

also complained of pain, dysphagia, facial nerve paralysis, or a cervical tumor. When the latter symptoms and signs were present, the diagnosis was carcinoma.

Culpability for Delay in Seeking Therapy.—Of 100 patients with parotid tumors, in all but 5 a history was available of the duration from the patient's observation of the mass until the time he first sought medical attention. Of these 95 patients, only 3 sought immediate medical attention. The others delayed from 6 months to 304 months. The average delay of all patients with tumors of the parotid gland was forty-two months (three and one-half years). Patients with benign tumors of the parotid gland delayed an average of forty-eight months (four years); patients with carcinoma delayed an average of thirty-eight and one-half months (three and two-tenths years). Of the group with carcinoma, only 2 patients sought immediate medical attention; delays in the others varied from two months to twenty-five years. Other authors have observed similar delays.[4, 42, 51] Thus a tumor of long duration may be a carcinoma, and the period of its presence may be no indication of its morbid anatomy.

The culpability in most instances lay with the patient who delayed excessively before seeking medical attention. Although most physicians instituted early treatment, their failure to understand the natural history of parotid neoplasms resulted in only partial excision of the tumor, frequently as an office procedure.

Location of Tumors.—There were 50 tumors on the right side and 50 on the left. Of the benign tumors there were 23 on the right side and 31 on the left; of the carcinomas there were 27 on the right side and 19 on the left side. These data demonstrate that there is no selectivity for either side in the benign or malignant tumors of the parotid gland. No instance of bilateral parotid involvement by tumor occurred.

Clinical Course.—Tumors of the parotid gland, both benign and malignant, are characterized by their slow growth; it usually takes one year or more before the average tumor reaches a size of 2 cm. The average duration of forty-two months before the patients seek medical attention characterizes the benign clinical course manifested by these tumors. In this series, in only 5 cases was there a history of rapid growth. Most of the patients complained of no symptoms other than the cosmetic deformity. However, 8 patients presented cervical metastases in addition to the primary tumor on admission. In most instances the tumors were located at the angle of the jaw, usually directly in front of the lobe but occasionally posterior to the lobe. Because of the embryologic development of the parotid gland (discussed later) with glandular projections in several directions, and because of the thin capsule about the gland in certain locations (retromandibular), parotid tumors may present in different locations. They may occur along the zygoma and at any locus in a region extending from the zygoma in a semicircular manner to the angle of the jaw and posteriorly to the mastoid process in addition to the pharynx. On physical examination the characteristic finding was a smooth, ovoid, firm mass which in many of the benign tumors was movable, and the overlying skin moved over the tumor. Attempts

to discern by physical examination whether the tumor was benign or malignant were very frequently misleading. Thus, carcinomas of the parotid gland may present a smooth, firm, freely movable mass within the parotid gland, which suggests benignity. The converse is also encountered where, because of an associated sialadenitis around a benign tumor, the presumptive diagnosis will usually be carcinoma. The size of the tumor, likewise, is no criterion in distinguishing a benign from a malignant tumor. The average size of the benign tumors studied here was 3.3 cm. in diameter, whereas the average size of the carcinomas of the parotid was 5.4 cm. in diameter. Although the average size for carcinomas was larger, mixed tumors may be massive (Fig. 1).

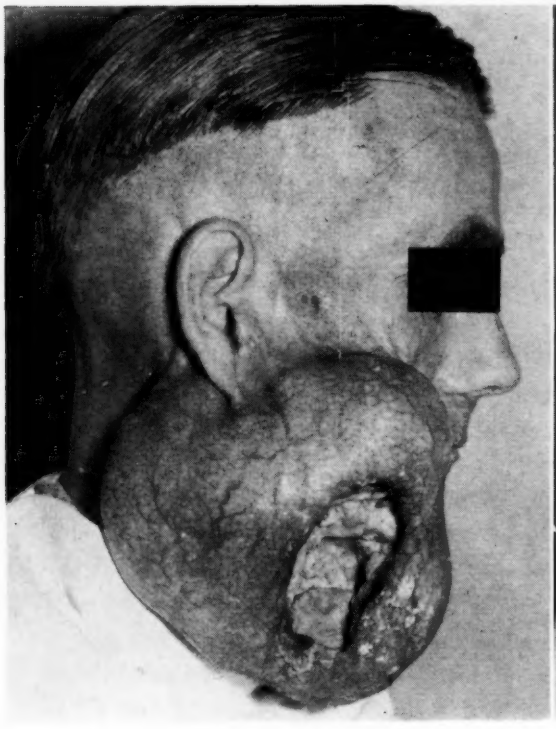


Fig. 1.

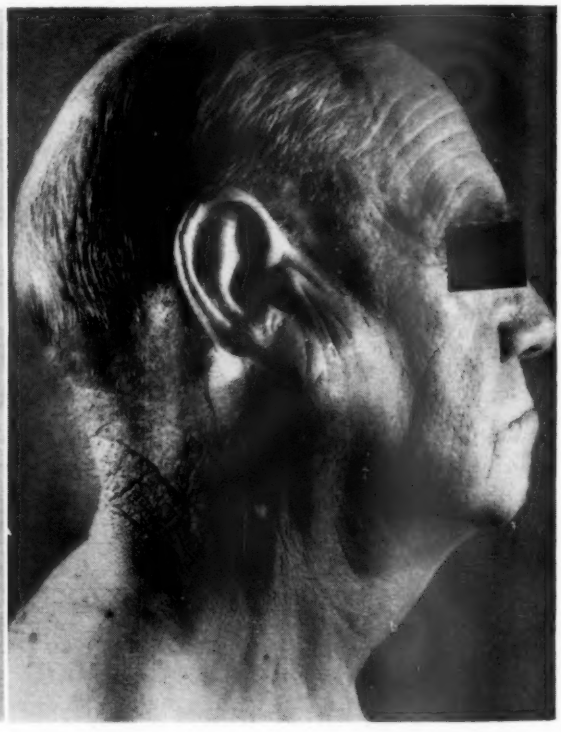


Fig. 2.

Fig. 1.—Clinical photograph of a massive mixed tumor which had been present for twelve years. It was resected by Dr. John Conley of the Head and Neck Department.

Fig. 2.—Carcinoma of the parotid gland which has extended into the pterygomandibular fossa and is fixed to the overlying skin.

In 6 patients the tumor arose from the retromandibular portion of the parotid gland, became localized between the posterior edge of the ascending ramus of the mandible and the mastoid process, and presented clinically as a poorly defined fullness rather than a discrete mass. Previous physicians had not suspected that this poorly delineated fullness was neoplastic. Thus, one must consider the possibility of a parotid tumor in all instances of fullness in this region.

GROSS PATHOLOGIC ANATOMY

Parotid tumors present a firm, grayish white, rounded mass, usually with a definite capsule. As the tumors grow the capsule may become thinned or

become invaded by tumor cells. If the tumor is superficial, it may grow into the subcutaneous tissue, being attached to the parotid gland by a rather narrow base. Certain benign parotid tumors in the superficial location may grow to massive sizes and present as a large pedunculated mass with thinned-out skin and often necrosis and secondary infection (Fig. 1). Tumors situated within the depths of the parotid gland will, with continued growth, compress the branches of the facial nerve. Benign tumors may grow to large sizes with consequent marked pressure against the facial nerve branches, but no instance has been encountered in which paralysis or paresis developed from this type of pressure. On the other hand, malignant tumors may infiltrate the nerve with ensuing facial paralysis. Whereas benign tumors tend to remain discrete, carcinomas will invade contiguous structures and, in advanced cases, will present a brawny fixed mass which is adherent to the parotid, overlying skin, and surrounding cervical tissues. They might become fungating and ulcerating. A neuralgia of the trigeminal nerve can occur from infiltration into the nerve. Extension of the tumor into the pterygomandibular fossa produces interference with jaw motion. Cervical metastases may occur. Although malignant tumors usually differ in gross appearance from the benign ones, it is frequently difficult to distinguish between the two types either clinically or at the time of operation. The presence of a definite capsule is no assurance of the benignity of the tumor. Careful microscopic examination not infrequently reveals infiltration of the capsule by tumor cells at one or more foci with extension of the cancer into the surrounding glandular tissue.

In several instances at the time of exploration the tumor was considered to be malignant because of marked induration about a solid tumor mass. In these instances the indurated gland was resected with the tumor mass and the benign nature of the tumor was established by microscopic examination, with the induration found to be due to an associated sialadenitis. In most instances it is clinically impossible to distinguish between a benign parotid neoplasm and one which is malignant (Fig. 2). In certain benign tumors such as papillary cystadenoma lymphomatosum the clinical and gross picture is such that a diagnosis of a benign tumor can usually be established.

DIAGNOSIS

Because of the difficulty in establishing a preoperative correct diagnosis, recourse must be had to additional data.

Sialography.—The instillation of Lipiodol into the parotid ducts and roentgenographic visualization of the gland give evidence of a mass within the gland. An anteroposterior view indicates its location (superficial or deep). Although Blady and Hocker[5] described how benign and malignant tumors could be identified by this technique, it has been found most difficult to distinguish one from the other. The technique is a distinct aid in identifying the nature of a mass in the parotid region and in distinguishing those which are extrinsic to the gland. Intrinsic masses can be further subdivided into inflammatory reactions with dilatation of the entire ductal system from a solid

mass within the gland containing no ducts but producing distortion of the surrounding ducts. This visualization indicates the location of the tumor and its relation to the facial nerve (whether superficial or deep) and aids in formulating the operative plan.

Cervical Lymph Nodes.—The presence of cervical adenopathy may indicate metastases from a parotid carcinoma, but caution must be exercised so that the nature of the cervical adenopathy is accurately determined. In several instances cervical adenopathy associated with a parotid mass was later found to be chronic lymphadenitis due to an intraoral infection which subsided with antibiotic therapy.

Another diagnostic pitfall is the presence of a small mass situated at the anteroinferior aspect of the parotid gland which is frequently mistaken for a primary parotid neoplasm. This may represent metastases from a silent intraoral primary cancer to the subfascial, extra glandular parotid lymph nodes. In other instances, lymphomas (Hodgkin's disease, and so forth) may present as a tumefaction in this locality.

Technique for Histologic Diagnosis.—The premise is accepted that a clinical diagnosis is often misleading; hence it cannot be utilized as criteria for therapy. In every instance a histologic diagnosis is obtained. The first attempt is an aspiration biopsy. This expedient procedure is performed rapidly as part of the physical examination and usually establishes the diagnosis. The aspiration biopsy is repeated if the first attempt is unsuccessful.

It is considered unwise to perform an incisional biopsy preceding operative intervention for fear of rupturing the capsule and inducing exophytic extension. Therefore, an exploratory incision into the parotid is made and a frozen section is performed. If this test is not diagnostic and the resection would involve sacrifice of the nerve, it is believed that the patient could be best benefited by closing the wound and awaiting the diagnosis from paraffin sections before proceeding with the radical operation.

METASTASES

Malignant parotid neoplasms metastasize by means of the lymphatics and the blood stream. In this series, metastases had occurred in 25 per cent of the cases when the patients were first observed. Eight patients had metastases to the cervical lymph nodes. The lungs were a frequent site of metastatic deposits, and occasionally many organs were diffusely invaded. Metastases from parotid cancer may sometimes adopt rather bizarre manifestations. In one observed patient the first metastasis to a lymph node occurred in the inguinal chain after which the patient demonstrated numerous discrete subcutaneous metastatic nodules. Another patient developed a subungual metastasis of the right middle finger, followed by metastases to the right axilla. The patient then developed pulmonary and cerebral metastases and died.

Another interesting feature of the behavior of metastases from parotid cancer is that in certain instances the metastases may grow wildly and the patient may die within a very short period. In other instances, especially the

cylindroma type, massive metastatic deposits may be observed in the lungs over a period of years and produce minimal symptoms (Fig. 3).

A subject of much speculation is the nature of metastases from so-called benign mixed tumors of the parotid gland. Brunschwig[8] and Kornblith[22] reported such instances; Mulligan[37] reviewed the literature and noted 21 instances of metastases arising from apparently benign tumors of the parotid gland. No such occurrence was observed in this series.

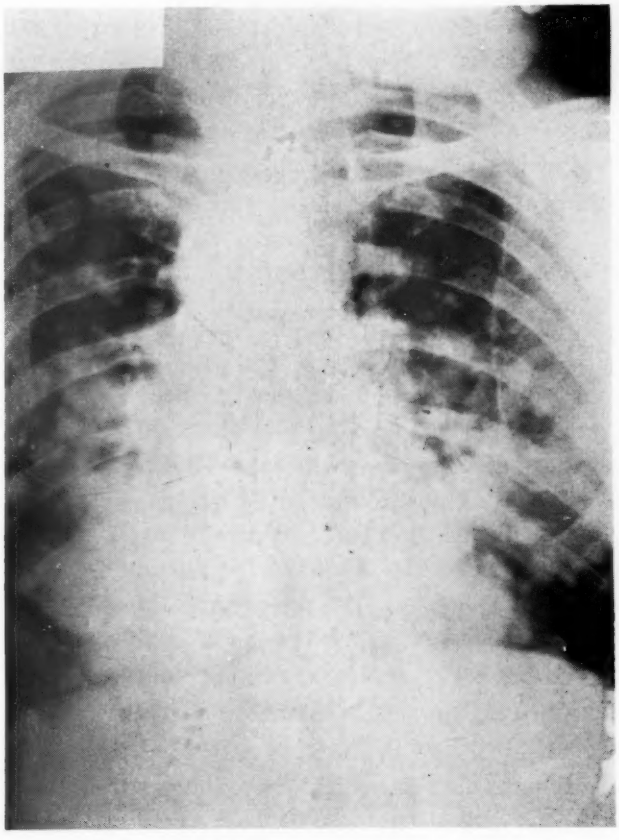


Fig. 3.—Roentgenogram of pulmonary metastases from a carcinoma (cylindroma type) of the parotid gland. Both lungs were diffusely involved but the patient had no symptoms when the roentgenogram was taken.

RECURRENCE OF THE TUMORS

Benign Tumors.—Of the 54 patients with benign parotid tumors, 34 were treated initially at the Pack Medical Group. Of these, 1 patient died postoperatively of a pulmonary embolus, 1 died from other causes one year after treatment with no evidence of parotid neoplasia, and 1 was lost to follow-up immediately after operation. Only 1 patient developed a recurrence three years after initial treatment here which had consisted of local excision and postoperative x-ray therapy. The recurrence was widely excised and interstitial gold radon seeds were inserted. This patient has remained free of disease for thirteen years. Of the remaining 30 patients, 17 were treated within the

past five years; thus 13 patients have remained free of recurrence for over five years.

Of the 20 patients whose referrals were subsequent to treatment elsewhere, in only 4 was the treatment adequate with the patients remaining free of tumor. The additional 16 were referred to this clinic manifesting recurrences an average of 4.2 years after the initial treatment (ranging from two months to ten years). Those recurrences which appeared early were undoubtedly persistence of tumor after inadequate treatment. Those whose clinical onset was delayed may possibly have had second primary neoplasms, but because of their indolent growth characteristics, the delayed recurrences may represent persistence of tumor after incomplete excisions. Recurrences were treated at the Pack Medical Group by wide surgical excision and usually postoperative irradiation. Two of this group developed a second recurrence which was adequately controlled by more radical surgical extirpation. In no instance was the facial nerve permanently damaged. These data attest to the adequacy of radical surgical extirpation and serve to develop criteria for treating primary mixed parotid tumors and their recurrences.

Carcinoma.—Of the 46 patients bearing carcinoma, 17 (37 per cent) presented evidence of recurrence an average of two and seven-tenths years from the time of attempted therapy; the range was from four months to ten years. Of this group of 46 patients, 33 had been treated elsewhere before referral, and of the 13 patients treated initially at this institution, 9 were referred with the neoplasm operable. There was a recurrence in 1 patient 15 months after operation.

There was nothing in the material studied to correlate a recurrence with the age of the patient, delay before therapy was instituted, the size of the tumor, or any feature of its histologic picture. The bulk of the evidence indicates that a recurrence is the result of inadequate extirpation.

Another factor of interest is the observation that recurrences usually retained the same histologic pattern as did the primary tumor. On occasion, however, a recurrence of a mixed tumor may be malignant. One such interesting occurrence was observed. A mass was removed from the base of the left parotid gland of a 33-year-old woman and was reported as a benign mixed parotid tumor. She was given postoperative radium therapy. A recurrence six years later revealed a mixed tumor of the parotid with suspicious malignant areas. She received postoperative x-ray therapy. Seven years after the excision of the first recurrence, a second recurrence presented itself and was widely excised. This recurrent tumor was a fully malignant adenocarcinoma. The patient has remained well and free of recurrence for sixteen years after resection of the parotid cancer.

Kirklin[20] reported that 34.3 per cent of the patients treated for a recurrence developed a second recurrence. This would seem to indicate that the distored tissue subsequent to an initial surgical attack hinders adequate dissection of residual tumor tissue.

It is stressed that because of the indolent nature of the growth of many of these tumors, long periods must elapse before a treated tumor can be considered cured, for recurrences have been observed ten years and more after treatment.

In no patient of this series was the opposite parotid gland involved by neoplasia, suggesting that parotid tumors most frequently arise from a solitary nidus, and recurrences indicate renewed growth after ineffectual extirpation rather than a proclivity of salivary gland to develop tumors. In an occasional case, multicentric foci can be observed in a given gland, but this is unusual.

Another cause for recurrences is spillage at the time of extirpation with seeding of tumor cells in the area. The presence of several small tumor nodules in the operative scar demonstrates such means of tumor propagation.

PROGNOSIS OF PAROTID TUMORS

It is difficult to evaluate the results of therapeutic attempts with parotid tumors because many of the tumors grow slowly and recur late, and because, as a result of the long interim necessary to observe these patients, many may be lost to follow-up. Furthermore, many patients are first seen in a state of extensive neoplasia (in this series, 35.7 per cent of patients with carcinoma), and nothing but palliation can be offered. In addition, previous attempts at treatment will have distorted the anatomic structures, and the treatment of a recurrence cannot be compared with the initial treatment of a primary tumor. The outlook is worsened with each recurrence.

The end results of the patients treated at this institution are tabulated in Table I. It will be noted that 39 patients were treated within the past five years. Of the 61 patients treated over five years ago, 25 of the 30 patients with benign tumors are alive and free of disease, an absolute survival rate of 83.3 per cent, and 10 of the 31 patients with carcinoma are free of cancer, an absolute survival rate of 32.3 per cent.

TABLE I. FIVE-YEAR END RESULTS IN 100 CASES OF PAROTID GLAND TUMORS*

		BENIGN TUMOR	CARCINOMA
Total number of patients	100	54	46
Number used for five-year survival (39 patients were treated too recently)	61	30	31
Number alive and free of disease five years or more		25	10
Absolute five-year survival rate		83.3 per cent	32.3 per cent
Number of patients lost to follow-up before five-year period		4	7
Relative five-year survival rate		96.2 per cent	41.7 per cent
Number on whom curative procedures were attempted (12 patients with carcinoma presented themselves too late)		30	19
Number used to compute therapeutic five-year survival rate (does not include 11 lost to follow-up and 12 on whom no curative procedure was attempted)		26	12
Therapeutic five-year survival rate		96.2%	83.3%

*Seen at the Pack Medical Group, New York, N. Y.

To evaluate the relative five-year survival rates, those patients who were lost to follow-up and were free of tumor at the time are subtracted from the total group. Since there is no way of ascertaining the fate of these people, the relative five-year survival rate is of value; in this series it is 96.2 per cent for the patients with benign tumors and 41.7 per cent for the patients with carcinoma.

Inasmuch as a certain number of patients present themselves with far-advanced cancer, including distant metastases, and since no curative procedure can be attempted on them, it is essential to subtract that group if an evaluation is to be made of the accomplishments of any therapeutic regime. In this series there were 13 patients with carcinoma who when first seen were considered incurable. If this group is subtracted in order to compute the therapeutic five-year survival rate, there are 12 patients with carcinoma on whom a therapeutic attack was made and who were followed for over five years. The therapeutic five-year survival rate for carcinoma of the parotid gland is then 83.3 per cent. Table II presents graphically the total experience of 41 patients treated for parotid cancer who were followed after treatment. Thirteen patients were treated too recently for five-year evaluation, and of the 28 patients followed for five years or longer, 11 survived (39 per cent). The discrepancy between this value and the 41.7 per cent relative five-year survival of Table I is due to the fact that patients who were followed for shorter periods are used for computation in Table II. The difference is not significant.

TABLE II. SURVIVAL RATES OF 41 PATIENTS WITH PAROTID CARCINOMA TREATED BETWEEN 1933 AND 1950 INCLUSIVE

YEAR	NUMBER OF CASES	YEARS OF SURVIVAL										REMARKS
		1	2	3	4	5	6	7	8	9	10	
1933	1	0										
1934	3	3	3	2	2	2	2	2	2	2	2	Two patients alive and well 10 and 16 years after treatment
1936	2	1	1	1	1	1	1	1	1	1	1	Well 14 years after treatment
1937	2	1	1	1	1	1	1	1	1	1	1	Well 13 years. (Other patient died 10 years after onset)
1939	2	2	2	2	1	1	1	1	1	1	1	Well 13 years after treatment
1940	4	4	2	2	2	2	2	2	1	1		One patient died at 7 years after treatment of other causes
1941	2	1	0	0	0	0	0	0	0	0		
1942	2	2	1	1	1	1	1	1	0			
1943	6	2	1	1	1	1	1					One patient died immediately after treatment (27 years after onset). Another was immediately lost to follow-up and presumed dead
1944	1	1	1									Lost to follow-up after 2 years
1945	3	3	2	2	2	2						One patient died of other causes at 1 year
1946	4	2	2	2	2							
1947	4	4	2	2								One patient died of lymphosarcoma at 16 months
1949	2	1										
1950	3	1										
Total cases	41	41	38	36	32	28	25	24	18	16	14	
Survival		28	18	16	13	11	9	8	5	6	5	
Per cent		68	47	44	41	39	36	33	33	37	36	

CLINICAL COURSE OF PATIENTS WITH CARCINOMA ANALYZED ACCORDING TO PATHOLOGIC TYPE

Malignant Mixed Tumor.—Eight such patients were treated at the Pack Medical Group. Of these, 2 are alive and well for eight and thirteen years, respectively. In two additional cases the period of treatment was too recent for evaluation. One patient is apparently free of tumor two years after treatment and another, one year after therapy. The malignant nature of this tumor is demonstrated in the case of 2 patients who died eight and fifteen months after treatment. In a third instance the patient died sixteen months after treatment because of malignant lymphoma. One additional patient died of heart failure postoperatively.

The exact nosology of malignant mixed tumors is not completely understood. The long history of 2 of these patients with presence of a mass of three years' duration followed by rapid growth for one year with pain of two to three months' duration suggests that malignant transformation within a mixed tumor had occurred. The clinical course may either be very slow (one patient presented a thirty-seven-year history with recurrences at ten- to twenty-year intervals) or extremely rapid, death occurring within one year after the onset of symptoms.

These tumors have a tendency to invade locally and sometimes grow to large size. Two of our patients presented the ominous symptom of facial nerve paralysis.

Some authors (Kirklin and associates[20]) do not believe in classifying such tumors as malignant mixed tumors but rather under the heading of the predominant cell type, such as squamous-cell carcinoma, adenocarcinoma, and so forth. The designation of malignant mixed tumor or carcinoma (squamous, adenocarcinoma and so forth) within a mixed tumor indicates the natural history of the specific neoplasm. The treatment, of course, should be radical surgical extirpation combined with neck dissection when a carcinoma is more than Grade I malignancy. Although these tumors are relatively radioresistant, postoperative gold radon seeds are indicated whenever infiltration into contiguous structures has occurred. If there is a possibility of residual tumor, the interstitial irradiation may be supplemented with external deep x-ray therapy.

Cylindroma.—There was only one patient bearing cylindroma observed here, and he was lost to follow-up. In other reported series cylindromas have constituted 4.7 per cent[20] and 3.2 per cent[42] of parotid tumors. They grow slowly but relentlessly. They invade locally, metastasize to regional lymph nodes (23.6 per cent), and also produce distant metastases. These tumors are relatively resistant, and although the initial response to x-ray therapy is good, recurrence is the rule.

Adenocarcinoma.—These tumors are more malignant. Of the 9 patients treated here, 5 have died from the neoplasms (55 per cent mortality), and death occurred rather rapidly (four and five months after treatment in 2

cases). Two patients presented the ominous symptom of facial nerve paralysis when first seen. These patients responded poorly to irradiation.

Squamous Carcinoma.—Of the 6 patients in this series 3 (50 per cent) died from the cancer. The course of patients bearing them is somewhat prolonged. One patient of this group died four years after the initial manifestation of the neoplasm and another, twenty-five years after the onset. The additional 3 patients are well four, six, and fourteen years, respectively, after the initial manifestation. Metastases develop early, and are frequently to the regional lymph nodes, less frequently to distant localities. Squamous carcinomas of the parotid gland, like epidermoid carcinoma elsewhere, are of moderate radiosensitivity and respond well initially to irradiation.

One patient in this series with squamous carcinoma of the parotid gland was treated exclusively by irradiation and has remained free of disease for sixteen years. He received 200 r. each day to a 7 cm. port (198 kv., 0.5 mm. Cu filter, 63 cm. target-skin distance) for a total of 4,000 r., after which he received interstitial radon seeds for a total dosage of 2,926 mc. hours. A small plastic operation was recently performed for a radiation ulcer.

Mucoepidermoid Carcinoma.—There were 4 patients bearing this interesting tumor first identified by Stewart, Foote, and Becker,[48] who described them as being either of very low-grade or very high-grade malignancy. These extremes in clinical course were observed in our 4 cases. One patient died seven months after treatment while the other 3 are apparently free of disease for three, four, and five years, respectively. These tumors are relatively radioresistant although Rawson and co-workers[42] describe beneficial effects in one such patient receiving x-ray therapy.

Undifferentiated Carcinoma.—This is a highly malignant form of cancer, and of the 12 patients observed here, 6 have died. Only 1 patient has survived four years; 2 died of other causes, 1 postoperatively and 1 seven years after treatment; 2 were lost to follow-up; 1 was treated too recently for follow-up study. Massive growths and regional lymph node metastases, as well as distant metastases to varied locations, are produced by this malignant neoplasm. The most radical attack, including both surgical extirpation plus interstitial gold radon seeds and external radiation therapy, must be administered to effect a cure.

Miscellanaeous.—The miscellaneous groups vary in malignancy from very benign lipomas and lymphocytic tumors to highly malignant adenosarcomas. The clinical behavior of sarcoma and melanoma in the parotid is similar to that of these neoplasms elsewhere.

TREATMENT

The data of this series demonstrate some lamentable shortcomings in the over-all treatment of parotid tumors and indicate routes of attack to overcome these shortcomings. Some of these are enumerated.

Errors in the Management of Mixed Tumors.—1. The slow growth of mixed tumors has lulled both patients and physicians into a false sense of

security concerning the benignity of these tumors. Thus, patients are first seen for treatment after long delays. During the delay a certain definite number of the tumors may have undergone malignant transformation and may be inoperable when first observed. In other instances the tumor may extend into the retromandibular portion of the parotid gland, making resection more difficult, or the tumors may grow externally (Fig. 1) to massive proportions. Although the latter are usually technically resectable with good end results, they do present a frightful appearance.

2. The belief that mixed parotid tumors are well encapsulated has led to the performance of local enucleation with resultant frequent recurrences. Some believe that there is no real capsule about the tumors and that the pseudocapsule consists of compressed parotid parenchyma. Regardless of the nature of the capsule it has been amply demonstrated that infiltration of the capsule by tumor cells occurs frequently. Accordingly, the capsule must be removed in every instance.

3. The previous fallacious teachings that larger tumors respond better to surgical extirpation have led to the dangerous practice of watchful waiting. All parotid tumors, as all tumors in every part of the body, should be removed with dispatch.

4. The performance of excisional biopsy without definitive treatment accounted for spillage and seeding of new foci of growths in certain instances.

5. The diffuse fullness of certain tumors (papillary cystadenoma lymphomatosum or retromandibular tumors) was not suspected of being neoplastic, and no treatment was instituted.

6. Lack of knowledge of the anatomy of the parotid gland and fear of dealing with the facial nerve have led to inadequate surgical excision. Recurrence is the rule. Past teaching indicates that this is a natural characteristic of mixed parotid tumors and that a recurrence should be expected. Parotid tumors exemplify an instance where inadequate medical efforts have camouflaged the natural history of a neoplasm, which false knowledge has more or less endorsed the inadequate treatment. It is our strong conviction that except in very few instances (mixed tumors with multicentric foci) a recurrence of a mixed parotid tumor reflects the inadequacy of the surgical attempt.

7. Certain soft parotid tumors, especially those which have undergone cystic degeneration, are misdiagnosed as cysts and are simply drained.

8. Small tumors are misdiagnosed as preauricular lymph nodes and no treatment is instituted.

9. Fear of producing salivary fistula has resulted in limited surgery. Only one such fistula was observed in this series.

10. Failure of certain surgeons to appreciate the limitations of irradiation for parotid tumors will cause them to leave residual tumor and to depend on postoperative irradiation to control the residuum. There are definite indications for radiation therapy for parotid tumors, but it should not be used as a crutch for inadequate surgery.

Errors in the Management of Parotid Carcinomas.—The major faults in the treatment of parotid carcinoma have been long delays before the institution of treatment, inadequate resection due to fear of damaging the seventh nerve, and a failure to recognize the malignant nature of the neoplasm. Furthermore, a lack of understanding of the lymphatic drainage of the parotid gland and the high incidence (25 per cent) of metastases to regional lymph nodes from parotid carcinoma have accounted for certain treatment failures.

Accordingly, the simple tenet for treating all parotid tumors is that they be adequately excised by sharp dissection. To accomplish this, a knowledge of the anatomy of the parotid gland and the facial nerve and of lymphatic drainage of the parotid is essential. Specific circumstances call for individual criteria for the extent of the resection. Each of these shall be discussed, including the role of irradiation for treating parotid neoplasms.

SURGICAL ANATOMY OF THE PAROTID GLAND

Embryologically the parotid gland develops as an outpushing from the angle of the mouth which extends toward the ear. When it reaches the vicinity of the mandible it sends buds superiorly, laterally, medially, and posteriorly, the primordial ductal system about which develop the glandular elements. Thus, in the adult the parotid salivary gland is irregular in shape. It extends superiorly along the zygoma, inferior to the angle of the jaw, and over the masseter muscle in a superficial position. The anterior surface is grooved by the posterior margin of the ascending ramus of the mandible, and the posterior extension protrudes between the pterygoid muscles toward the pharynx in the so-called retromandibular (pterygomandibular) space. The inner surface drops deeply into the neck by two large processes; one goes behind the styloid process toward the mastoid process and may attach to the sternomastoid muscle, and the other process extends behind the articulation of the lower jaw.

It is thus evident that parotid neoplasms may develop anywhere on the side of the face: along the zygoma, on the cheek, in front of or below the ear, in the retromandibular fossa, in the stylomastoid recess, about the mastoid at the sternocleidomastoid origin, and into the pharynx. This description further illustrates the difficulty in attempting to remove each vestige of parotid tissue.

An extension of the superficial cervical fascia envelops the parotid gland and is continuous with the fascia of the masseter and the sternomastoid muscles. From the viewpoint of tumors, several characteristics of the fascia are important. (1) It varies in thickness in different positions. The retromandibular part of the gland is almost devoid of fascia, permitting tumors of this region to grow readily toward the pharynx and giving those tumors which present in the pterygomandibular fossa an appearance of diffuse fullness rather than that of a discrete mass. (2) The capsule is thickened over the anteroinferior aspect, thus producing a sense of tenseness of tumors of this location. (3) Some tumors grow beyond the capsule and are attached to the gland by a narrow stalk. (4) The enveloping fascia sends small fibrous strands through-

out the gland, dividing the glandular elements into myriads of tiny lobulations interconnected by innumerable fibrous septa. The importance of this will be discussed in relationship to the surgical anatomy of the seventh nerve.

THE SURGICAL ANATOMY OF THE FACIAL NERVE

The surgical anatomy of the facial nerve has dominated every attempt directed at treating parotid tumors. It is of interest that the change in thinking pertaining to the relationship of the facial nerve to the parotid gland has been from one school of teaching which taught that the nerve was so intimately imbedded in the gland that it defied efforts to extricate the gland from the nerve, to the present trend which attempts to attribute an oversimplification of the relationship of the nerve to the gland. McWhorter,[30] McCormick, Cauldwell, and Anson,[25] and more recently State[46] have described the parotid gland as consisting of superficial and deep lobes connected by a narrow isthmus. They described the nerve as passing between the two lobes, but not actually penetrating the parotid capsule, and lying within the parotid parenchyma. The nerve was described by these authors as having the same relationship to the two parts of the parotid gland as a bookmark has to the two pages of a book it separates (State[46]) or as the "meat in a sandwich" (Bailey[2]). Our numerous dissections have failed to confirm this concept. In every instance the nerve was found to have passed through the parotid fascia and to lie directly within the parotid parenchyma. Martin[32] has also described this relationship. In no instance were separate lobes of parotid encountered separated by fascial envelopes with the nerve traversing this hypothetical space. If one unfamiliar with the relationship of the facial nerve to the parotid gland attempts to dissect the parotid neoplasm expecting to find the nerve lying between two separated parotid lobes, he will be uniformly disappointed, and the further progress of the dissection may be affected.

It may be mentioned that ontogenetically the nerve, after emerging from the stylomastoid foramen, separates into two branches at a point where a small nubbin of parotid tissue exists. With the development of the parotid gland, two superficial projections, one growing inferiorly and the other superiorly, and two deep projections, growing superiorly and inferiorly, respectively, develop and fuse intimately at about the eighth week of prenatal life, thus completely embedding certain portions of the facial nerve within the parotid parenchyma.

The parotid gland can readily be dissected away from the seventh nerve, essentially because of the differences in consistence. The flaccid, yielding, spongelike consistence of the parotid glandular tissue, which is bound together by innumerable tiny fibrous septa, can readily be peeled away from the firm, taut nerve which traverses it. One might envision the pouring of a sticky wax over the nerve which on hardening could have its superficial portion easily removed. Likewise, the deeper portion posterior to the nerve and those trabeculations which extend into the various anatomic recesses of this location could only be removed piecemeal.

The facial nerve emerges from the stylomastoid foramen and runs anteriorly with a slight inferior inclination through a small potential space anterior to the mastoid process, at which point it traverses the parotid gland (Fig. 4). Shortly after traversing the gland it bifurcates into the temporofacial and cervicofacial divisions. Occasionally this bifurcation will occur before the nerve enters the parotid substance (Fig. 5). Numerous divisions then occur within the parotid gland. Whereas the main trunk of the nerve measures about 3 mm. in diameter when it enters the gland, about five to seven small filamentous branches take exit from the anterior border extending over the masseter muscle to their various points of innervation. The small mandibular marginal branch takes exit from the inferior border of the gland and travels within the platysma swinging inferior to or beyond the horizontal ramus of the mandible to innervate the lower lip. Whereas most of the other branches have numerous cross-anastomoses and damage to one branch will frequently be corrected by an anastomotic branch, the marginal branch has no such anastomoses, and its severance will always result in paralysis of the corresponding half of the lower lip.

LYMPH NODES OF THE PAROTID GLAND*

The parotid nodes are divided into three principal groups: (1) superficial-suprafascial, (2) subfascial-extraglandular, and (3) deep intraglandular (Fig. 6).

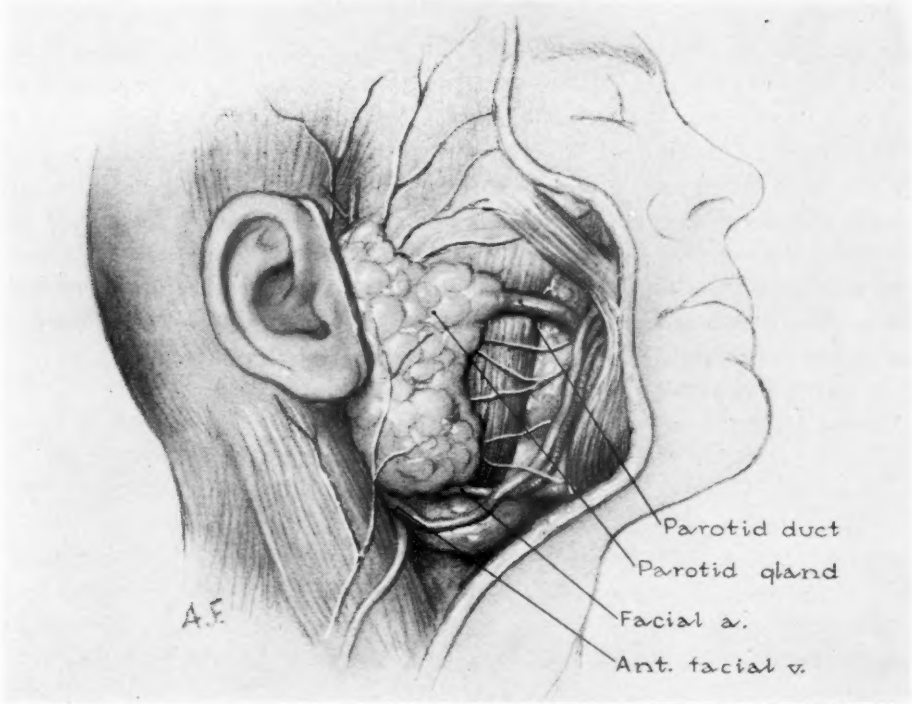
1. *The Suprafascial Parotid Nodes.*—These nodes exist in one-third of the cases; their number varies from one to four, and the size is in inverse proportion to their number. They are always preauricular and placed in the neighborhood of the tragus. The nodes are sometimes situated opposite the notch which separates tragus from antitragus, or else above the tragus. In the latter case, the nodes are always placed against the superficial temporal blood vessels, sometimes behind, sometimes lateral to, but rarely in front of, these blood vessels.

2. *The Subfascial-extraglandular Nodes.*—In this group are included the lymph nodes contained in the parotid sheath and placed immediately below the fascia. Some of these nodes are placed anteriorly, in front of the auricle, (a) the anterior or preauricular. The others, (b) inferior or infra-auricular, lie at the inferior extremity of the parotid gland.

(a) *The subfascial preauricular nodes:* There are usually one or two, but there may be as many as four. They are placed between the fascial covering and the external surface of the parotid gland, sometimes near the tragus and sometimes rather at a distance from it in front of the auricle. Normally there exists but one subfascial node near the tragus, whereas the neighboring subfascial nodes are frequently absent. The parotid gland occasionally partially conceals certain subfascial preauricular nodes; in that case, the latter are always placed at some distance in front of the auricle, along the anterior limit of the

*After Rouviere.[43]

Fig. 4.



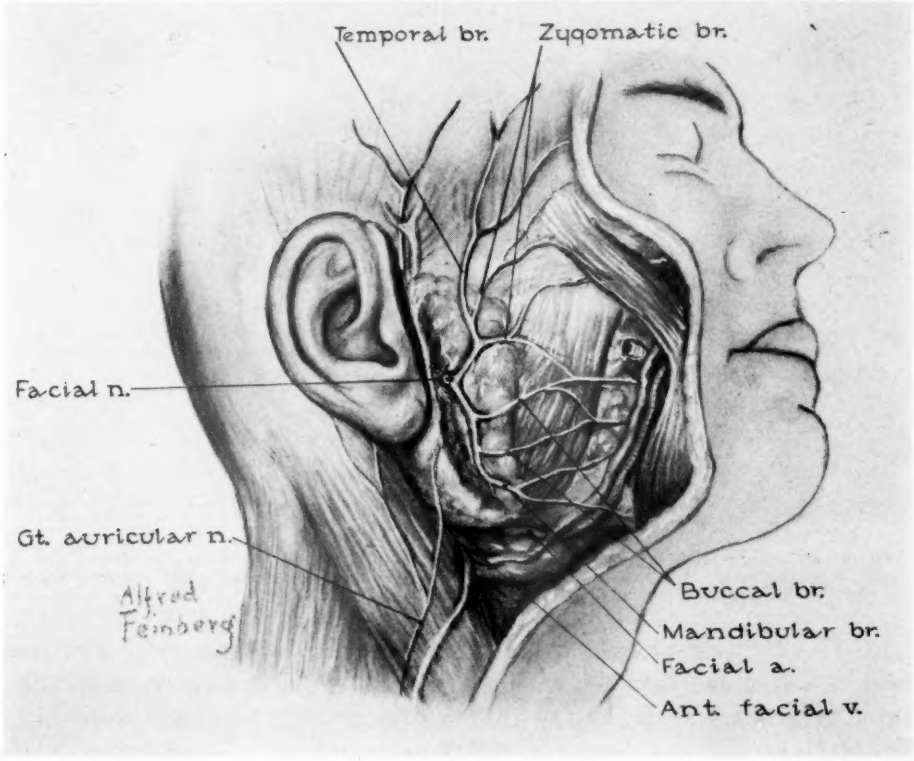


Fig. 5.

Fig. 4.—Illustration demonstrating the relationship of the parotid salivary gland to the facial nerve. The posterior portion of the nerve is buried within the gland. The terminal branches of the facial nerve emerge superficially from the anterior border of the parotid gland to their various sites of innervation. The great auricular nerve can be observed ascending over the sternocleidomastoid muscle and coursing over the superficial surface of the parotid gland.

Fig. 5.—Illustration demonstrating the course of the facial nerve through the parotid gland. The nerve, shortly after emerging from the stylomastoid process, penetrates the parotid gland and is intimately bound by the glandular parenchyma. The superficial portion of the gland can be easily dissected away from the nerve, but the deeper portion must be removed piecemeal.

superficial lobe of the parotid gland. This disposition of the nodes is due to the mode of development of the parotid gland. In fact, before the gland is completely developed, the external surface of these lymph nodes is in contact with the fascial covering of the parotid gland, but because of the manner in which the superficial lobe of the parotid gland extends during its development in nearly all directions, and particularly in front, the glandular tissue insinuates itself between the fascial covering of the parotid and the external surface of the lymph nodes, concealing the latter totally or partially. In the first instance, the lymph nodes become the deep intraglandular parotid nodes, and in the latter case they assume the location referred to previously.

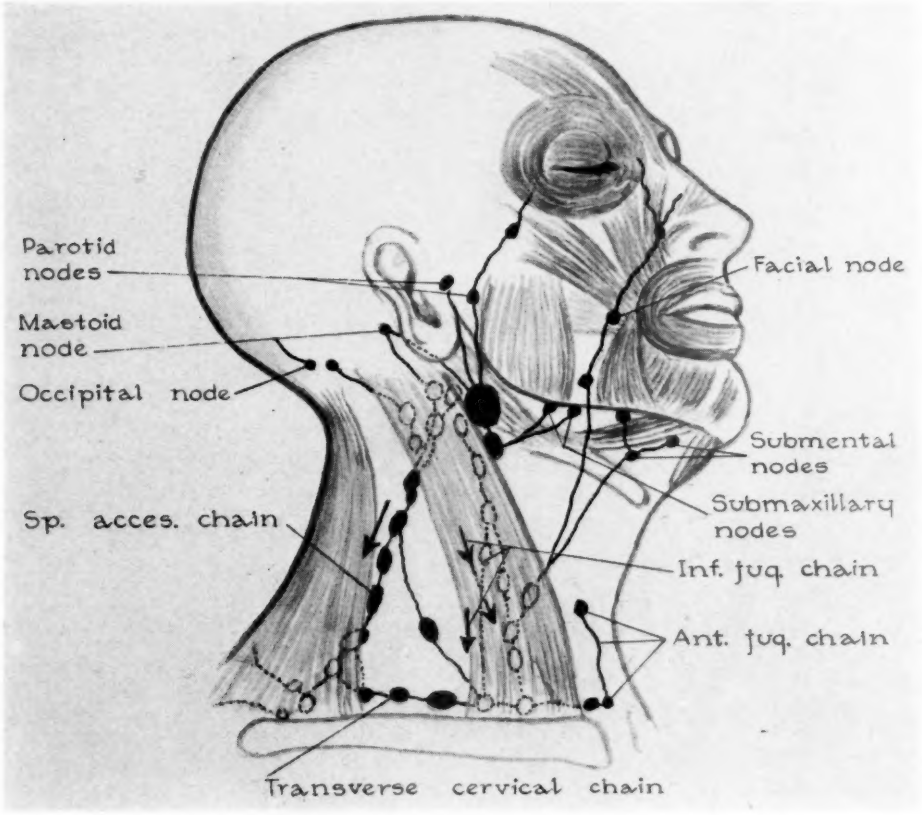


Fig. 6.—The cervical lymph nodes, indicating the routes of drainage from the parotid gland and demonstrating the need for a radical neck dissection to treat metastases from parotid carcinoma to the cervical lymph nodes (after Rouviere).

(b) *The inferior parotid infra-auricular nodes:* These are a group of one to three nodes situated in the region of the external jugular vein, at the point at which this blood vessel leaves the parotid gland. They are covered by the superficial layer of the deep cervical fascia and are placed between the inferior extremity of the parotid and the anterior border of the sternocleidomastoid muscle, from which they are separated by the sheath of the latter muscle, while above and below the nodes are separated from the parotid glandular tissue by a thin layer of fibrocellular tissue only. This fine layer

of tissue is sometimes thickened, particularly in the adult and the aged person, and may assume the aspects of a fibrous membrane, in which case the nodes appear enclosed in a reduplication of fascia. In the newborn child, this group of nodes ascends, like the parotid gland, behind the lobule of the ear.

3. *Deep Intraglandular Nodes.*—In the fine cellular tissue which unites the superficial with the deep lobes of the parotid gland, four to ten lymph nodes are always found. This number does not include the minute nodes nor the periacinar lymph elements which can be revealed on microscopic examination only. The deep nodes are grouped around the external jugular and posterior fascial veins in the region, chiefly, where the facial crosses the external jugular vein. They are placed sometimes on the inner and sometimes on the outer side of the nerve rami and also more often and in greater number on the outer than on the inner side of the nerve. It is not uncommon to find a few nodes at some distance from, and in front of, or behind, the external jugular vein. The deep nodes are located most often in the cellular tissue which separates the two lobes of the parotid gland, but they are sometimes partly or wholly surrounded by the glandular tissue of one or the other lobe. At times there exist one or two nodes along the external carotid artery, either before this artery enters the parotid gland or in the tissue of the deep lobe.

OPERATIVE TECHNIQUE FOR RESECTING PAROTID NEOPLASMS

The amount of tissue to be removed surgically will depend on many factors and will vary from a simple extracapsular local excision to a total parotidectomy with sacrifice of the facial nerve and radical neck dissection in continuity. The various indications will be discussed.

Two fundamental processes considered essential for any operative procedure are (1) that the histologic nature of the tumor be determined and (2) that wide surgical exposure be obtained for every case, with the possible exception of certain subcutaneous tumors arising from the periphery of the gland and which are 1 cm. in diameter or less. In such instances a small incision over the tumor may be made with local excision of the tumor, including its capsule. In all other cases the operative exploration to be described is utilized, and the decision as to the extent of the procedure is determined on the basis of the histologic picture and the morbid anatomy encountered (Figs. 7 to 17).

It is advisable always to forewarn the patient concerning the possibilities of facial nerve paresis or paralysis. In no instance of our experience has the facial nerve been accidentally severed. The existence of temporary facial paresis is common, and unless the patient has been forewarned of its occurrence, its recognition will be alarming.

Anesthesia.—Endotracheal general anesthesia is routinely employed. The choice of anesthetic agents is a matter of individual preference. The patient is draped in such a manner that the entire half of the face on the involved side is visible. This permits visualization of the muscle contractions when the nerve branches are stimulated. General anesthesia permits this observation,

and since local anesthesia does not, it should never be used except in the most unusual cases although its use is technically feasible.

Incision.—The Y incision is used almost exclusively (Figs. 7 and 8). The lobe of the ear is retracted upward. The posterior component of the incision permits adequate exposure for dissecting the main branch of the facial nerve, entrance into the pterygomandibular space, and removal of the mastoid tip and sternocleidomastoid muscle where indicated, and facilitates the completion of a radical neck dissection when performed. The anterior component of the incision facilitates the dissection and isolation of the terminal seventh nerve branches. These two incisions join under the tip of the lobe, and the incision is continued inferiorly parallel to the stenocleidomastoid muscle for a variable

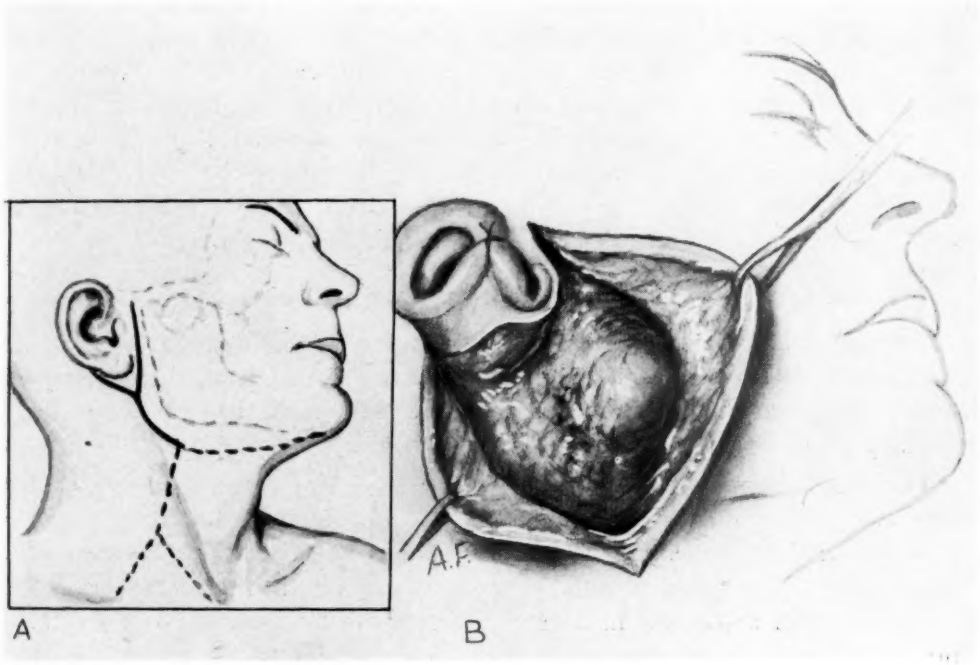


Fig. 7.—*A*, The Y-shaped incision utilized for practically all parotid gland explorations. The broken lines indicate the incision extended to perform a radical neck dissection in continuity with a parotidectomy. *B*, The ear is dissected superiorly and sutured away from the operative field. The skin flaps are being developed.

distance, depending on the location and extent of the neoplasm, usually one fingerbreadth (1½ cm.) inferior to the angle of the mandible. This has been a convenient landmark for exposing the external carotid artery shortly after its bifurcation, and frequently in parotid resections its ligation helps to minimize bleeding. Skin flaps are developed (Fig. 7). The facial flaps are thin and continue anteriorly to the location where the facial branches emerge from the parotid gland. The posterior flap is dissected to expose adequately the mastoid process and the tip of the sternomastoid muscle. The posterior portion of the parotid gland occasionally presses intimately against the upper portion of the sternomastoid muscle. The gland is easily separated from the muscle unless involved by cancer, and by retracting the gland anteriorly a potential space is developed in the depths of which is the main branch of the seventh cranial nerve.

At this point the decision can usually be made as to the nature and extent of the operative procedure required. It may consist of (1) a simple extracapsular excision of a mixed tumor, (2) excision of that portion of the gland superficial to the facial nerve (so-called superficial lobectomy[46]), (3) a subtotal parotidectomy with excision of the deeper portion of the gland for certain recurrent tumors, (4) a parotidectomy with preservation of the facial nerve combined with a radical neck dissection, (5) a radical parotidectomy with sacrifice of the facial nerve, and (6) radical parotidectomy with resection of a portion of the ascending ramus of the mandible.

Fig. 8.—Clinical photograph showing the Y incision sutured.

There are some who may believe that this exposure is too extensive for mixed tumors of the parotid which appear small on clinical examination. When it is recalled that many parotid tumors are like icebergs with only a small portion of the total presenting superficially and the main mass being present in the depths of the gland, the need for adequate exposure becomes apparent. Dissection under direct observation will permit complete extirpation of the tumor regardless of how deep it extends and will further permit preservation of the seventh nerve. When one further recalls the high recurrence of mixed parotid tumors, usually the result of inadequate surgery, and the ensuing difficulty of resecting a recurrent tumor, the somewhat larger exposure is definitely warranted.

A modification of this incision must be utilized for certain parotid cancers which have infiltrated the skin. In these instances the skin and subcu-

taneous tissue must be excised in continuity with the parotid gland, and radical neck dissection performed. The resulting defect is closed with skin graft (Figs. 16 and 17).

Fig. 9.

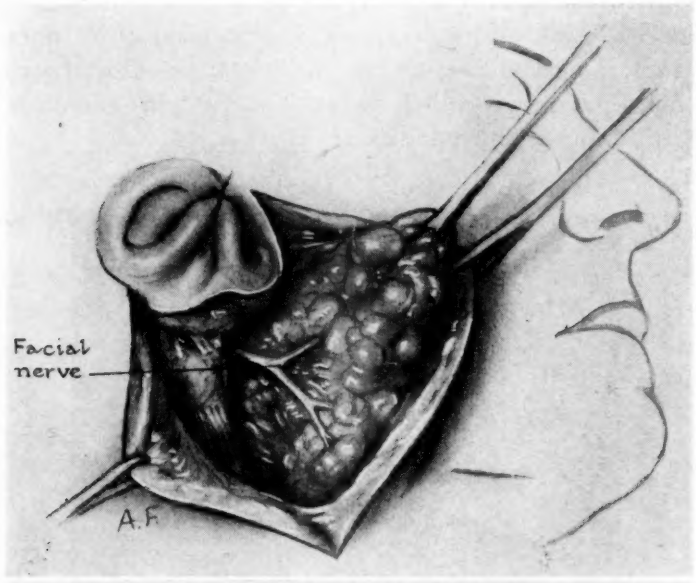


Fig. 10.

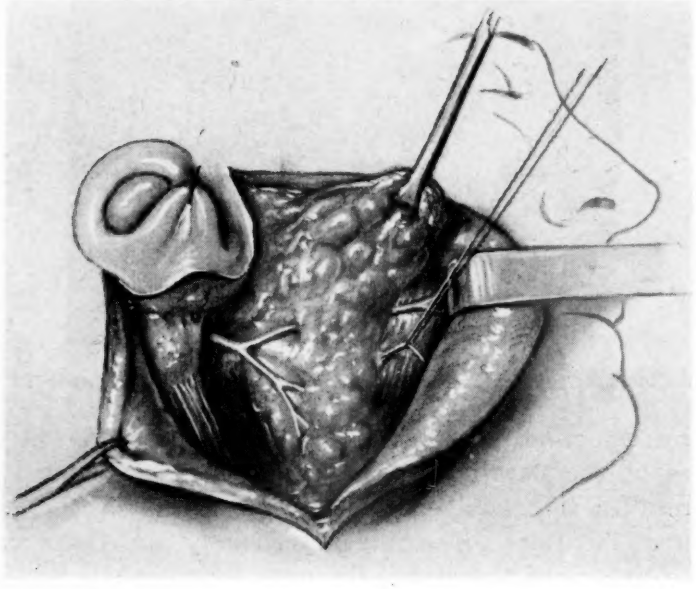


Fig. 9.—The parotid gland has been dissected away from the mastoid process and sternocleidomastoid muscle. The nerve is quite deep (1.25 to 2 cm. from the skin) and is the only nerve bisecting the plane of the incision and traversing the operative field from a posterior origin, anteriorly. It measures from 2 to 3 mm. in diameter. By gently teasing the gland anteriorly the main branch of the seventh nerve and its divisions can be brought into view.

Fig. 10.—Technique utilized in separating an associated sialadenitis about a parotid tumor from the facial nerve. A piece of silk suture or a nerve hook is placed around the main trunk and around the terminal branches of the nerve, which permits dissecting between the immobilized nerve. The gland can be separated by blunt dissection if adherence is due to an inflammatory reaction. In our experience it could not be freed by blunt dissection if adherence is due to cancer, in which case it is sacrificed.

Exposure of the Facial Nerve.—Three methods have been described for exposing the seventh nerve. They consist of (1) first isolating the marginal mandibular branch and tracing it to the main stem, or (2) tracing one of the branches as it emerges from the anterior border of the parotid back to the main branch, or (3) identifying the main branch first as it comes out of the stylomastoid foramen. After having utilized all three methods we are convinced that the easiest and most direct way is first to isolate the main branch. The easiest method of exposing the facial nerve is to deepen the incision along the upper portion of the sternocleidomastoid muscle at its origin in the mastoid process. By dissecting in this plane it is almost impossible to damage the nerve. The origin of the posterior belly of the digastric muscle into the mastoid is an additional aid in identifying the nerve, for it presents itself just superior to this point. As the dissection continues for a distance of 1½ cm. the nerve will be encountered extending at almost right angles from the stylomastoid foramen, swinging beneath the external auditory canal to extend superficially to the anterior surface of the ascending ramus.

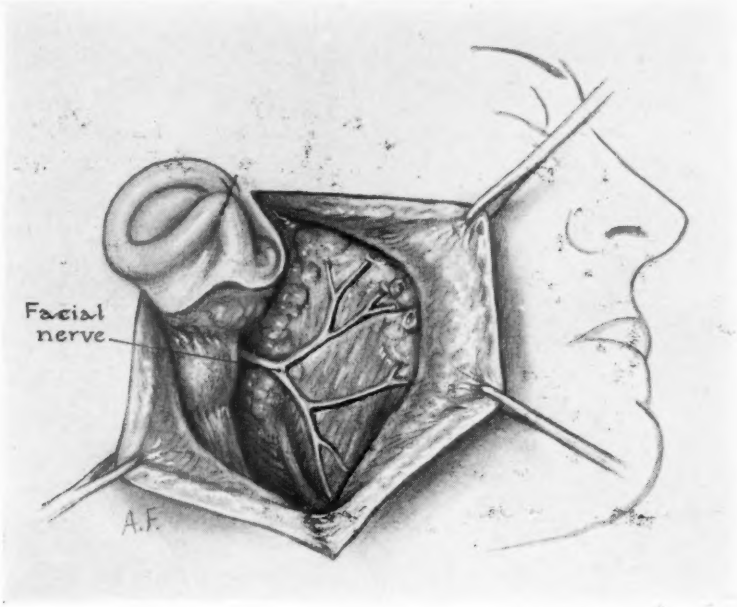


Fig. 11.—The dissection completed. Vestiges of parotid gland remain.

Practically all nerves in this vicinity travel in a more or less vertical direction, while the facial nerve travels almost at right angles to the vertical plane of the incision. By following the anterior border of the sternomastoid and deepening the incision by gently dissecting the posterior portion of the parotid gland anteriorly, the nerve will be encountered extending in the direction of the dissection, that is, from posterior, anteriorly (Fig. 9).

An aid which has been found helpful in certain short-necked patients with long overhanging mastoid processes is to remove a portion of the mastoid with the osteotome, which affords additional room for dissection.

Dissection of Tumor.—The superficial portion of the parotid gland can now be dissected free of the nerve with relative ease. The peculiar pliable consistence renders it dissectible. The gland is dissected anteriorly, and as the dissection continues the nerve will be found to divide into its component branches. By continuing the dissection to the anterior margin, the entire portion of the gland superficial to the facial nerve can easily be removed. Since most of the

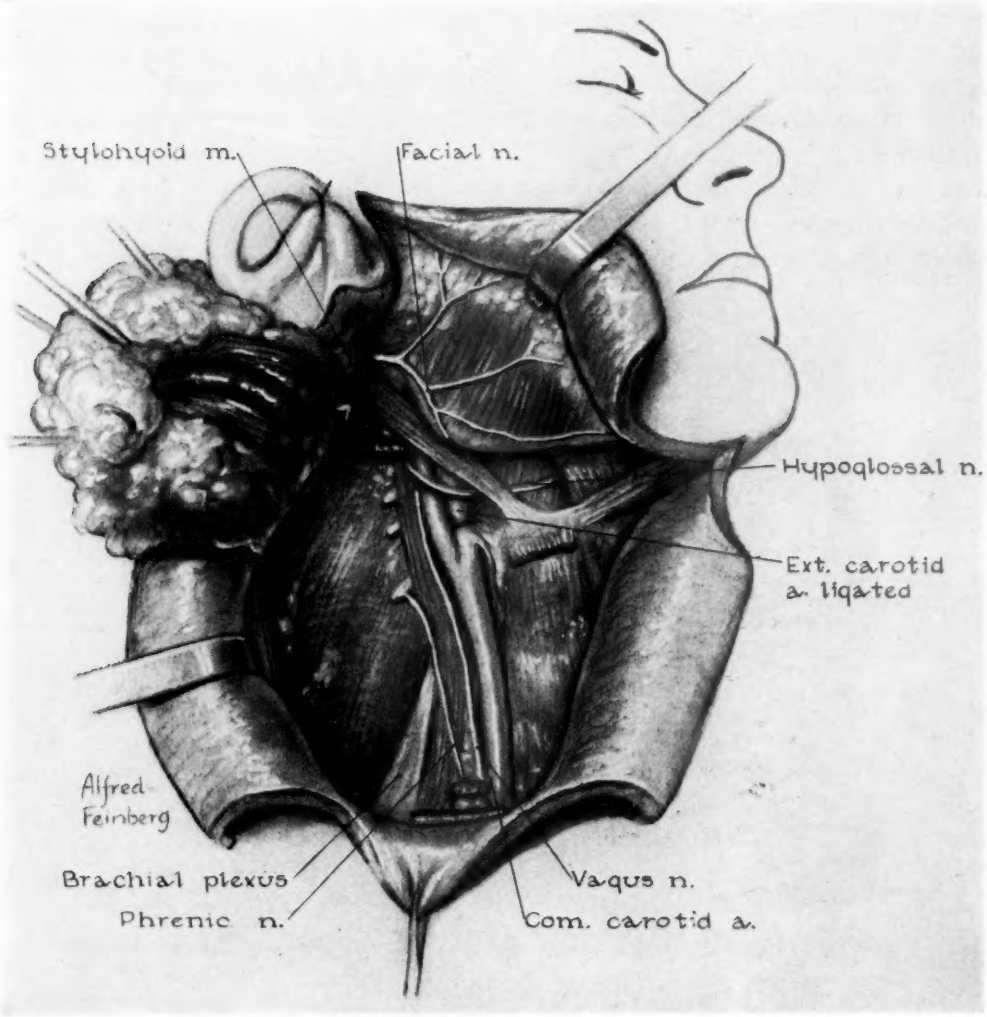


Fig. 12.—Combined parotidectomy and radical neck dissection in continuity. The nerve may be spared in occasional instances of low-grade carcinoma which had produced metastases to cervical lymph nodes.

mixed tumors occur in this location, this procedure will permit adequate resection of the majority of mixed parotid tumors. If it is not desired to remove the entire superficial gland, an extracapsular local excision of the tumor can be performed adequately under direct vision. If the tumor extends posteriorly between the branches of the nerves (we have never seen mixed tumors infiltrate

the facial nerve; instead they distort the nerve by pushing it aside as tumor growth continues), the tumor can be readily dissected into the posterior portions of the parotid gland.

In certain instances the presence of a mixed tumor may induce an associated sialadenitis which may present a clinical picture of cancer. When operating on recurrent mixed tumors, the associated inflammation and adhesions so distort the tissues that it is difficult to distinguish where the tumor

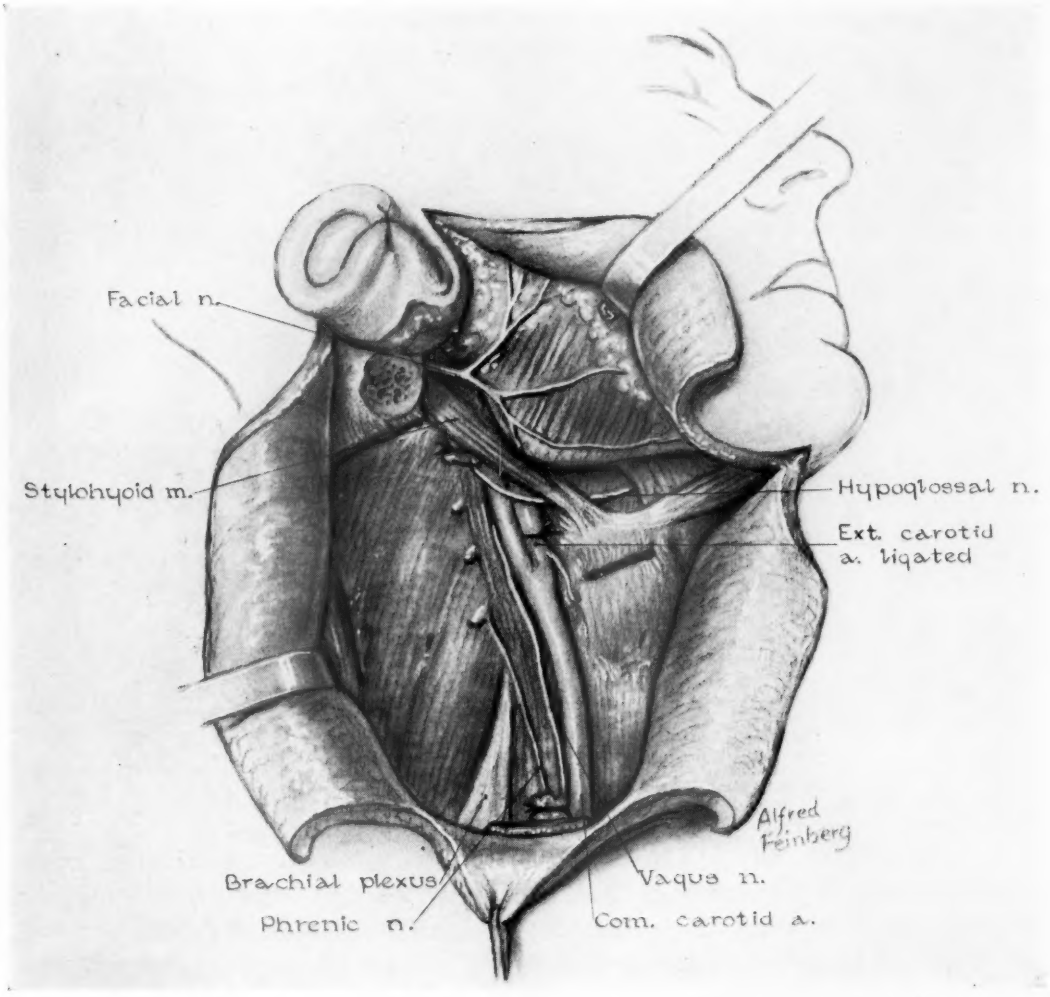


Fig. 13.—Combined parotidectomy and radical dissection completed. Note the ligated external carotid artery to help minimize bleeding. This is performed at the beginning of the operation. A portion of the mastoid process has been removed to afford better exposure. The stylohyoid muscle may be removed.

ends and scarring begins. Certain of these cases give a mistaken impression of carcinoma invading the nerve. A useful technique for dealing with these situations is to identify the nerve branches as they emerge from the gland by keeping these branches taut by either a nerve hook or a small piece of silk and placing a similar piece of silk under the proximal branch, thus immobiliz-

ing the nerve. Each branch can then be dissected separately, free of the surrounding tissue. In every instance where this was performed and where the distorted parotid tissue could be dissected free by blunt dissection, the pathologic report was always sialadenitis. Contrariwise, when the nerve branches could not be isolated by blunt dissection, cancer was always present. This simple technique has been found most useful in deciding if the nerve should be severed, or which of its branches should be severed, in the presence of parotid cancer (Fig. 10).

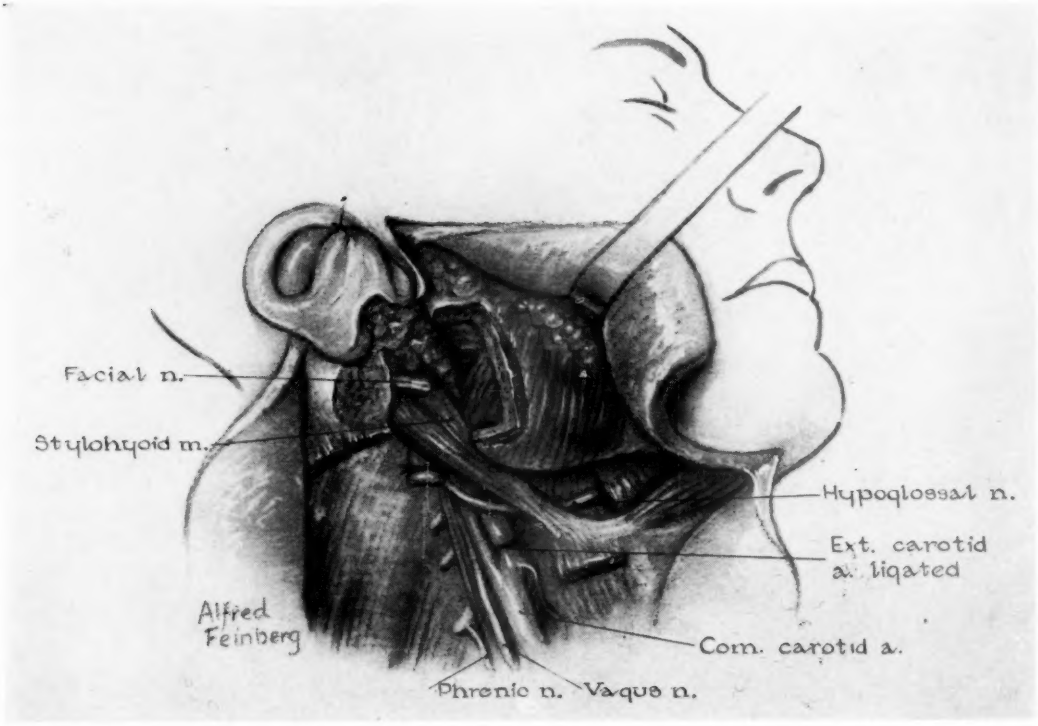


Fig. 14.—Combined parotidectomy and radical neck dissection with a portion of the ascending ramus removed to permit entering into the pterygomandibular fossa and removing the posterior portion (deep lobe) of the parotid gland. The facial nerve has been sacrificed.

Treatment of Parotid Carcinoma.—Admittedly, the best method of treating cancer of any organ is radical extirpation of that organ, sacrificing any intervening structures which interfere with a block dissection and removing the regional lymph nodes in continuity. The parotid gland lends itself well to such extirpation except for certain prolongations of the gland within anatomic recesses. The sacrifice of the facial nerve certainly facilitates the resection, and theoretically this should be accomplished for all cases of cancer. The resultant deformity is great, and in certain instances, especially in younger patients, we have violated the tenets of cancer surgery and have performed the parotidectomy leaving the seventh nerve in situ. This procedure seems warranted in certain low-grade carcinomas developing in mixed tumors (the so-called malignant mixed tumor), in certain discrete cylindromas, and in squamous-cell, adeno-, and mucoepidermoid carcinomas of low-grade malignancy. The technique of separating the parotid tissue from the nerve by blunt dis-

section is utilized, and if it can be accomplished, the nerve is not sacrificed. However, if any branch cannot be so dissected free, that branch is severed. If the main trunk cannot be easily freed, the entire nerve is resected.

The seventh nerve is never spared for undifferentiated carcinoma or any carcinoma which is diffusely infiltrative. Usually no attempt is made to spare the nerve for recurrent cancer except for very low-grade carcinoma. The failure of recurrence when this technique has been practiced is encouraging, but it must be realized that it is a clinical compromise with the disciplines of cancer surgery, and continued critical observation of these patients must be maintained for proper evaluation and a possible change in the practiced technique, if indicated.

Fig. 15.—Technique of reconstructing the paralyzed face after severance of the seventh nerve (after Brown). Temporal fascial slings are utilized.

Neck Dissection.—The high incidence of metastases to regional lymph nodes from parotid cancer (25 per cent of this series) emphasizes the need of resecting these nodes in continuity with the primary tumor. The parotid gland lends itself well to this procedure.

The lymph node distribution is presented in Fig. 6. The rich network of nodes in the vicinity of the parotid gland favors rapid dissemination to this chain. The dissection should always include all the preauricular and subauricular lymph nodes. It should extend posteriorly to excise the mastoid node, and it is advisable to extend the dissection further posteriorly to include the occipital nodes. An occasional metastasis to this site has been noted. The abundance of lymph nodes about the parotid facilitates dissemination to all cervical nodes, and then nothing short of a complete radical neck dissection should be accomplished.

It may be mentioned that the lymph nodes to be excised during a complete neck dissection for a primary tumor of any location of the head and neck should include the suprafascial, glandular, and subfascial parotid nodes. To accomplish their removal it is necessary to resect the inferior portion of the parotid gland and the contiguous tissue, which includes this group of lymph nodes.

Technique of Combined Parotidectomy and Radical Neck Dissection.—The essential steps are graphically shown in Figs. 12 and 13. The incision is extended as shown by the dotted line in Fig. 7. The contents of the submaxillary triangle, the jugular vein, and spinal accessory nerves are routinely removed. The external carotid artery is usually ligated at the beginning of the operation; the stylohyoid muscle is usually removed but may be preserved. The sternocleidomastoid muscle must be removed at its origin, and frequently the mastoid process is removed with an osteotome.

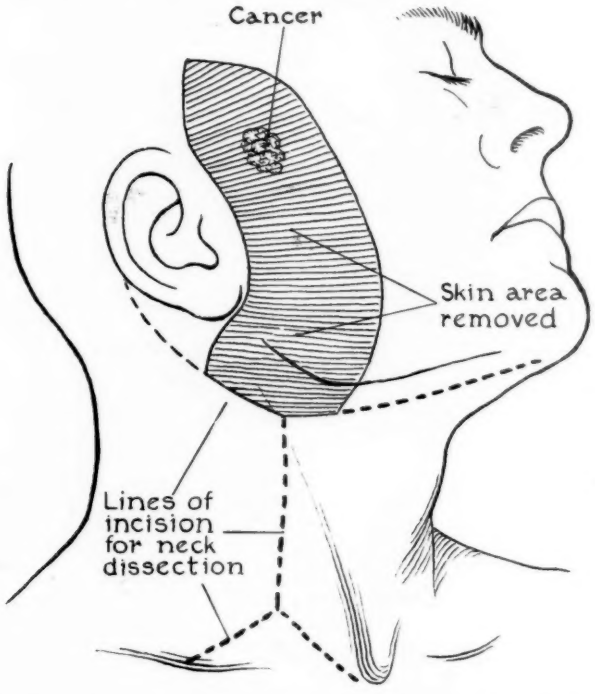


Fig. 16.—Combined parotidectomy and neck dissection necessitating, in addition, removal of a large portion of skin because of dermal infiltration of a parotid cancer.

The Mandible and Tumors of the Parotid Gland.—The mandible frequently presents a formidable obstacle in treating certain parotid tumors. The parotid gland is visualized hugging the posterior border of the ascending mandibular ramus with extension anterior (forming the superficial lobe, the site of most tumors) and a posterior extension into the retromandibular fossa. The mandible must be surgically manipulated for (1) parotid tumors which arise from the posterior portion of the parotid gland when the possibility exists that they have extended posterior to the mandible; (2) any tumor arising from

that portion of the parotid gland in back of the mandible (so-called deep lobe). These tumors fill the retromandibular (pterygomandibular) space and require special surgical consideration; (3) carcinomas which invade the mandible.

Surgical Techniques for Operation on the Mandible in Its Relationship to Parotid Neoplasms.—

1. *Tumors extending posterior to the mandible:* A simple method of exploring this region is to remove a block of bone from the posterior portion of the ascending ramus. Frequently the tumor will be exposed and its excision effected (Fig. 14). If the tumor should extend beyond the area exposed, it is necessary to sever the ascending ramus with a Gigli saw, and by retracting the severed portion of bone, access is afforded to the pterygomandibular space. The severed bone ends are wired or plated together at the finish of the operation. Very little functional incapacity is experienced by the patient.

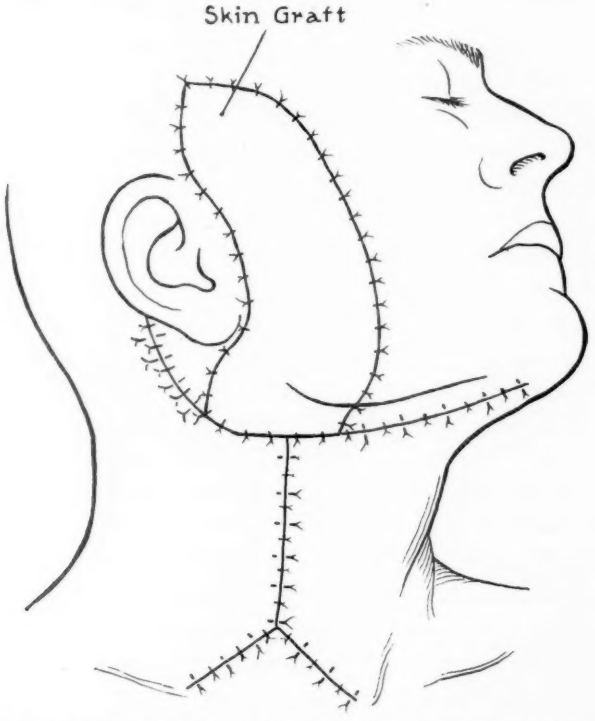


Fig. 17.—The operation described in Fig. 16 completed with a split-thickness skin graft utilized to cover the defect.

2. *Tumors of the retromandibular (pterygomandibular) space:* This potential space, bounded by the mastoid proces, the ascending ramus of the mandible, the vertebral column, and the pharynx, is relatively inaccessible to the surgeon. The important structures which traverse this space are the parotid gland, internal carotid artery, internal carotid vein, and the ninth, tenth, eleventh, and twelfth cranial nerves. Since this space is almost entirely encased in bone, tumors which arise here either present in the space between the posterior border of the ramus and the mastoid or they bulge into the pharynx. If a mixed tumor of the retromandibular portion of the parotid

gland presents into the pharynx, it may be removed by the intraoral route as described by Ehrlich.[12] If the tumor is malignant or if it presents posteriorly, it must be resected by the external approach.

The incision is the same as previously described. The mandible is skeletonized and transected with a Gigli saw, and separation of the ends affords access to this space. If the tumor is not adherent to the mandible, it may be removed in toto by this exposure.

3. *If the mandible is invaded by the neoplasm* a hemimandiblectomy combined parotidectomy and radical neck dissection is accomplished. If roentgenographic evidence of mandibular destruction is apparent, then it is best to disarticulate the involved side of the mandible and perform a complete hemimandiblectomy combined with radical parotidectomy and neck dissection.

IRRADIATION OF PAROTID TUMORS

The role of irradiation has not been truly assessed as a therapeutic agent for treating parotid neoplasms. Although most of the parotid tumors are radioresistant, cures have been obtained by treating parotid cancer exclusively by irradiation. The picture has been confused by the fact that radiotherapy has been applied to neoplasms after they have become widespread, infiltrating contiguous structures, and as a crutch for inadequate surgery. If there was a recurrence after this regime the surgeon was not blamed because it was usually agreed that the irradiation was not great enough, and if there was no recurrence it would be impossible to assess the role of irradiation in effecting the cure. It is impossible to compare the results of excision alone to those obtained by surgery combined with irradiation because in most instances the practiced surgery was not complete. Nothing can be gained by comparing an inadequate surgical procedure to results obtained from surgical treatment combined with irradiation. Thus, Smith and Stenstrom[45] quoted the poor results obtained from surgical resection by Benedict and Meigs (96.7 per cent failure), MacFee (81 per cent failure), and others. In contrast they purported to show that better results have been obtained by Ahlbom, who used irradiation either exclusively or combined with surgical excision and obtained a 25 per cent five-year survival, and Cade, who obtained a 27 per cent five-year survival for carcinomas treated by radical surgery plus postoperative irradiation.

It is believed that irradiation (both interstitial and external) has a definite place in the treatment of parotid neoplasms, but it is necessary to define that place accurately and to use irradiation intelligently and aggressively whenever indicated. Conversely, it is believed that sole reliance upon irradiation for operable parotid tumors should be condemned.

In this series, of the 13 patients with primary carcinoma of the parotid gland who received initial treatment here, 1 patient was treated exclusively by interstitial gold radon seeds, and he remained well and free of disease for seven years after which time he died from other causes. One other patient was treated by external x-ray therapy and interstitial radon seeds, and he has sur-

vived for over sixteen years with no signs of recurrence. These data demonstrate that parotid cancer can be cured by irradiation in certain instances. Two other patients who are apparently cured were treated by radical excision alone, and 2 others were treated by excision plus postoperative irradiation. In past years, irradiation had been used quite frequently; at present, most reliance is placed on surgical removal, and as more time elapses the results of surgical intervention can be evaluated.

It is believed that in the treatment of benign tumors sole reliance should be placed upon adequate surgical extirpation. However, because the parotid gland may have projections into areas which are relatively inaccessible (such as the depths of the stylomastoid notch and certain recesses of the pterygomandibular space) gold radon seeds are always available in the operating room. If the tumor is in the vicinity of one such recess, it is considered advisable to insert interstitial gold radon seeds into these sites. Gold seeds 0.3 mm. in diameter and containing 1 to 1.5 mc. of radon are inserted into the proper site. The total dose depends on the size of the sphere to be irradiated and varies from 600 to 2,200 mc. hours. No additional irradiation is given.

The indications for x-ray therapy for mixed tumors are: (1) operable tumor for which the patient refuses surgical intervention, or if operation is contraindicated for other reasons; (2) postoperatively after incomplete excision, especially after an attempted surgical excision of a recurrence; (3) inoperable tumors. After numerous recurrences the tumor may be so mutilated that operation is contraindicated. In such instances response to irradiation is usually poor.

Ahlbom advocates preoperative irradiation, believing that it facilitates operation by making the capsule firmer. We cannot subscribe to this policy.

The x-ray factors usually employed were 200 to 250 kv., 15 to 30 Ma., 0.5 mm. Cu filter, 30 to 50 cm. target-skin distance; the size of the portal varied with the tumor in question and averaged 6 by 9 cm. One hundred fifty roentgens were given to each of two portals daily for a total dosage of 1,500 to 1,800 r., measured in air, to each of three ports.

Irradiation of Parotid Cancer.—Most parotid carcinomas are radioresistant. However, cures may on occasion be obtained by this type of therapy.

Indications for irradiation of parotid cancer: (1) operable cancer for which the patient refuses operation, or if operation is contraindicated for other reasons; (2) if the complete resection would involve sacrifice of the facial nerve and the patient refuses this defect. As much of the tumor as possible should be resected and a combination of interstitial radon and external x-ray therapy applied. The surgeon should not advocate this practice but must resort to it as a compromise regime; (3) after a radical parotidectomy certain remnants of parotid tissue remain in inaccessible anatomic recesses which were not too distant to the cancer. These areas should receive interstitial gold radon seeds and a course of postoperative deep external x-ray therapy; (4) inoperable carcinoma; (5) postoperatively for all instances of undifferentiated carcinoma. The results of this group by surgical intervention

alone are poor; (6) the presence of distant metastases. Both the primary site as well as the metastases should be irradiated.

It is believed that reliance should be placed on surgical removal for parotid tumors. This group of neoplasms, although resistant to irradiation, does respond to radiation therapy sufficiently to warrant its use whenever surgical intervention is contraindicated or inadequate. The role of this form of treatment has not yet been exactly determined.

SUMMARY AND CONCLUSIONS

1. The clinical features of 100 patients bearing tumors of the parotid salivary gland are presented.

2. Parotid tumors comprised 0.5 per cent of all patients bearing neoplasms treated at the Pack Medical Group. Of the 100 patients, 54 bore benign tumors, and 46 suffered from carcinoma.

3. The average age of all patients was 45.2 years. Although the peak incidence of patients with benign tumors was less (36.1 years) than patients with carcinoma (52.9 years), there is so much overlapping in the ages of the two groups that the age of a given patient cannot be utilized as a diagnostic criterion.

4. The most frequent presenting symptom is the presence of an asymptomatic mass in the vicinity of either ear.

5. The diagnosis of benign or malignant tumor cannot be made clinically (except in advanced cases), and a biopsy must be taken to determine the type and extent of the surgical intervention required.

6. Indications and techniques for surgical extirpation of parotid neoplasms are described which have been developed on the basis of the surgical anatomy of the parotid salivary gland, the anatomy of the facial nerve, the lymphatic drainage of the parotid salivary gland, and the natural history of neoplasms arising from this organ.

7. The role of irradiation in the treatment of parotid neoplasms is described, and it is emphasized that radiation therapy should not be used as a crutch for inadequate surgical removal but should be used for its specific indications.

8. The data are analyzed to discern the cause for frequent recurrences in the past, and these features are discussed.

9. Of the 54 patients with mixed parotid tumors, 31 per cent developed recurrences. Of the 34 patients treated initially at this institution, only 1 developed a recurrent tumor. Of the 46 patients with carcinoma, 37 per cent presented a recurrence an average of 2.7 years from the time of attempted treatment.

10. The absolute five-year survival rate for the benign tumors is 83.3 per cent and for carcinoma, 32.2 per cent. The relative five-year survival rate for benign tumors is 96.2 per cent, and for the malignant neoplasms it is 41.7 per cent. The therapeutic five-year survival rate for patients with parotid cancer is 83.3 per cent.

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Surgical Technique

CHOLEDOCHOJEJUNOSTOMY EN ROUX Y

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CHOLEDOCHOJEJUNOSTOMY en Roux Y has proved to be a satisfactory surgical procedure for control of chronic recurring pancreatitis.[6-8] Eleven patients have received the operation at Kennedy Veterans Administration Hospital. All except one have remained free of attacks. The eleventh patient suffered one slight attack during an alcoholic bout, but has been symptom-free since 1948. Several cases have been followed for as long as four to five years.

The control of pancreatitis achieved by this operation strongly suggests that Opie's[1] concept of the etiology is correct. This concept involves regurgitation of bile into the pancreatic duct under pressure. Experimental production[3] of pancreatitis also presents evidence in favor of this theory. The benefits from sphincterotomy, advocated by Doubilet, Mulholland,[2] and others, are gained by avoidance of this regurgitation. Choledochojejunostomy severely tests the validity of this concept because the operation cannot possibly permit any change of function except deviation of bile from the pancreatic duct and duodenum.

The operation, however, has not been universally accepted because of assumed technical difficulties, and it is considered "too radical" by many surgeons, who would otherwise employ the procedure. Consequently, these operators seek a more simple procedure. The main criticism concerns the formation of stricture at the site of the common-duct intestinal anastomosis, which in effect would produce common-duct stricture, a dreaded and obstinate anatomic deformity. Another unfounded criticism involves surgical work in the face of enlarged, indurated, edematous pancreas and peripancreatic inflammation. Actually, the occasional small size of the unobstructed duct is the only threatening difficulty. One stricture occurred twenty-two months after the operation. This stricture was easily corrected by resection of the strictured anastomosis, and reanastomosis was performed. The ease of the reanastomosis was evident because the obstruction had induced dilatation of the common duct. This patient has remained free of trouble for more than one year, which suggests that the duct will probably remain free of stricture formation.

It should not be necessary to call attention to the fact that this type of anastomosis must be used in all pancreaticoduodenectomies and has been

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successfully used by many[4, 5] for correction of common-duct strictures and accidental injury of the common duct during gastric resection for ulcer or tumor. Recent reports of stricture formation for this operation in the previously mentioned conditions are notably lacking, particularly if the Roux Y principle is employed. The Roux Y principle establishes a defunctioned loop, which creates a situation where infection around the anastomotic area and in the common duct is either minimal or entirely absent.

I have received numerous requests for a description of the technique of this operation by surgeons who hesitate, but who are eager, to employ it. It must be stated that I claim no originality in the technique briefly described later; although minor variations may be present, these are regarded as variants existing in the maneuvers of different surgeons. One routine rule can be stated however: the choledochojejunal anastomosis must be accomplished by the insertion of very few sutures. It is believed that numerous silk sutures, many of which are unnecessary, will invoke a local foreign-body fibrosis extensive enough to lead to stricture formation. Reinforcement must not be achieved by "piling on" interrupted silk sutures. If a suture is not accomplishing a job, it is better to remove it.

When choledochojejunostomy has been selected for control of pancreatitis, we proceed as follows:

1. Dissect common duct and place tape around lower end. It is not necessary to trace the duct under or into pancreatic tissue because the length of common duct is sufficient.

2. Perform cholecystectomy in usual manner.

3. Transect jejunum between Kocher clamps about ten to twelve inches below Treitz's ligament.

4. Close end of upper jejunal segment with interrupted fine black silk sutures.

5. Partially close end of lower jejunal segment allowing opening large enough to "fit" lumen of common duct.

6. Transport lower end of jejunum through an opening in transverse mesocolon.

7. Transect common duct as low as possible and ligate or transfix lower end.

8. Begin choledochojejunal anastomosis by placing a posterior row of interrupted atraumatic 00 catgut sutures between the common duct and jejunum. Make certain that there is mucosa-to-mucosa suturing. These are drawn up and tied so that the knots reside in the lumen. Four or five sutures will suffice.

9. Make small stab wound in anterior jejunum about one and one-half inches below choledochojejunal anastomosis. Place T tube as indicated in diagram (Fig. 1).

10. Close anterior part of anastomosis with interrupted fine black silk sutures. Knots are obviously outside of lumen. Stitches do not include mucosa, if possible.

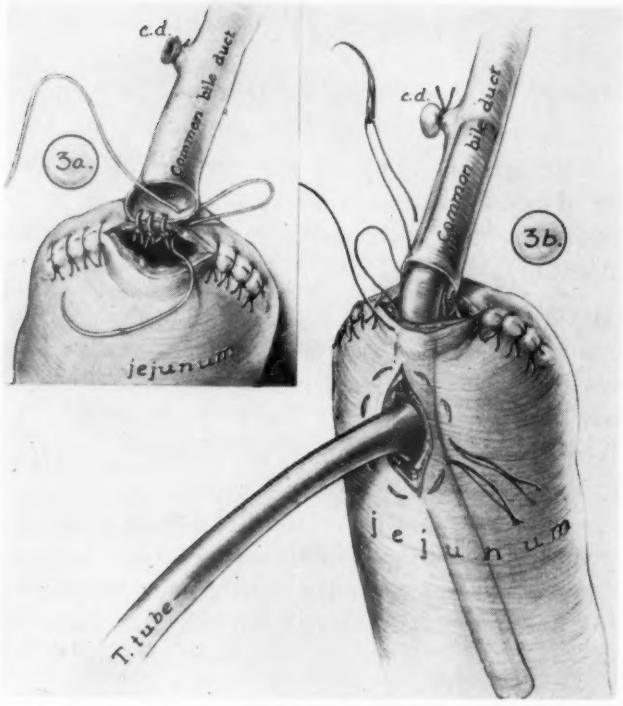

Fig. 1.—Sketch showing details of anastomosis and method of placing T tube.

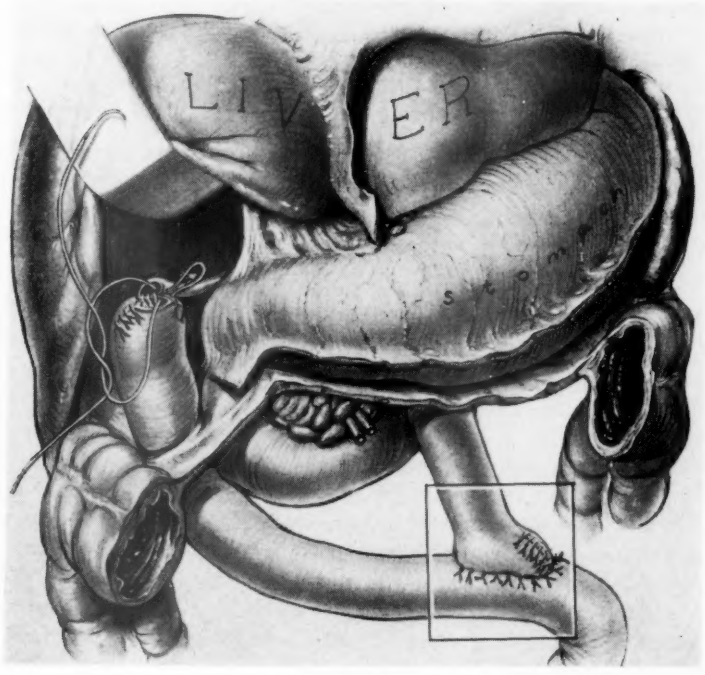

Fig. 2.—Sketch showing general plan of operation.

11. Suture jejunum to liver or round ligament or any available structure which pulls jejunum toward liver to relieve any possible tension on suture line.

12. Suture transverse mesocolon to jejunum to prevent herniation of intestinal loops.

13. Perform enteroenterostomy at site twelve to eighteen inches below choledochojejunal anastomosis.

Lateral anastomosis has been used in our cases, but end-to-side is proper if preferred by operator.

14. Reapproximate mesenteries.

15. Place drain lateral to choledochojejunal anastomosis.

The postoperative care is the same as for common-duct exploration. The T tube is allowed to remain in place for three months. It must be gently irrigated once daily to prevent collection of "mud." Cholangiogram is taken before removal to assure soundness of anastomosis.

It may not be necessary to leave the T tube in place for three months. There is a difference in thickness of the wall of the common duct compared to that of the jejunum, and perhaps the T tube permits more uniform luminal formation. One patient removed the tube on the thirteenth postoperative day without ill effect. The drain is usually removed in stages from the fourth to seventh day.

The procedure requires two to three hours of operating time.

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Book Reviews

Anatomy of the Autonomic Nervous System. By G. A. G. Mitchell. Pp. 356. Edinburgh and London, 1953, E. & S. Livingstone.

Professor Mitchell, director of the anatomic laboratories at the University of Manchester, has been publishing descriptions of the autonomic plexuses for nearly twenty years in the British journals. To this reviewer, who has followed his work from the beginning, Mitchell's illustrations and text have been pre-eminent in this field of neuro-anatomy. Now, happily, these studies have been expanded into a book. This volume contains a singularly simple, clear description of the complicated peripheral pathways of the craniosacral and thoracolumbar plexuses, together with chapters on their embryologic development and central representation within the brain and spinal cord. At a random sampling from the index, it is seen that practically nothing that the surgeon would want to ask the neuro-anatomist has been omitted. The 131 figures comprise a series of superb colored and half-tone illustrations, photomicrographs, and photographs of the author's dissections. Apart from the manifest skill with which these were made, their accuracy is attested to by Sir James Learmouth, who states in his foreword that even in the finest branches no doubtful strand was accepted "as nervous unless its nature was proved by microscopic examination."

The bibliography contains over 800 references. Professor Mitchell deserves high praise for the way he has done justice to the extensive and often conflicting literature that has grown up in this complex field, especially regarding the central nuclei and fiber tracts. In view of the especially confusing problems concerned with the hypothalamus, the reader will relish the following admission from so distinguished an anatomist: "Anyone who suffers from the delusion that anatomy is an effete subject with no problems left to solve is advised to read even a tithe of the bewildering conglomeration of literature on the hypothalamus and its connections. If he does, delusion will be replaced by disillusion."

In the opinion of the reviewer this book is a stimulating product of the British school of anatomy at its best and should appeal particularly to American readers.

Pathologische Physiologie der frischen geschlossenen Hirnverletzungen, insbesondere Hirnerschütterung: klinische, anatomische und experimentelle Befünde. By Dr. R. Wanke, Professor of Surgery at the Universität Kiel. Pp. 196, with 90 colored illustrations. Stuttgart, 1948, Georg Thieme Verlag.

This book is a relatively complete treatise on the pathologic physiology of head injuries. The author has included considerable clinical data along with experimental material in an attempt to understand better the physiologic processes produced by various types of brain lesions. He has included pathologic changes in the liver, in the lungs, in the kidneys, and of the blood, as well as those of the brain. He has attempted to interpret many of the clinical manifestations of such lesions in the light of the pathologic physiology found. Throughout the book there are many charts and graphs explaining these variations, and as an addendum there are color illustrations of the pathologic processes found in the lung and in the brain. Many of his final conclusions are similar to those generally accepted; for example, he believes that blood pressure changes are the most constant clinical findings in patients with increasing intracranial pressure. However, there are considerable data regarding blood sugar levels, porphyrin studies, body temperature regulation, and so forth, in patients and experimental animals with cerebral lesions. The book is written in an involved literary style and is very difficult to translate from the German. To be certain the translation was correct, the book was offered to, and read by, a physician trained in Germany. He also had difficulty, at times, in establishing the author's intent. It is felt that the book is of no particular asset

to the average investigator or clinician, but would be of distinct value to anyone willing to spend long hours at translation in order to obtain a few pertinent points of the pathologic physiology of the brain.

Shoulder Lesions. By H. F. Moseley, D.M., F.R.C.S., F.A.C.S. Ed. 2. New York, 1953, Paul B. Hoeber, Inc. $12.00.

Every author should have a publisher like this one, and every publisher, such an author. This book sets a standard in medical publishing. The type, illustrations, and arrangement make the book a pleasure to read. Contained within it are many of the colored plates on the shoulder previously distributed by the drug houses. Many of these beautiful drawings could be used to great advantage in other medical books. In spite of the quality of the book, its price has remained reasonable. The author's material, selected almost entirely from his own experience, gives the work a tone of quiet assurance. By limiting the scope of the book, the author remains in command of the subject throughout. The final chapter is the weakest and emphasizes the faults of many of the recent "regional" books without detracting from this one. This is probably the best book on the shoulder to be published since Codman's classic.

Reconstruction Surgery and Traumatology. Edited by Max Lange, Vol. 1. Basel, Switzerland, 1953, S. Karger.

This marks the first of a series of annual volumes in the field of reconstructive surgery and traumatology. The Editorial Board contains outstanding surgeons throughout Europe, several from South America, and from the United States. It is an attempt to bring together a variety of opinions based on widely divergent experience.

The initial volume deals with three subjects: intramedullary nailing, the late results of fractures of the neck of the femur, and reconstructive operation for nerve paralyses. The high caliber of the presentations can be judged by a partial list of authors: Küntscher, d'Aubigné, Böhler, Scaglietti, Bunnell, Steindler, and Lange. If such a group of presentations can be assembled each year, this will undoubtedly become one of the more important annual publications in its field.

Tumors of Bone, A Roentgenographic Atlas. Annals of Roentgenology, Vol. 21. By Bradley L. Coley and Norman L. Higinbotham. New York, 1953, Paul B. Hoeber, Inc. $10.00

This volume contains a well-selected and well-reproduced sample of x-ray pictures of bone tumors and of bone diseases simulating bone tumors. There are occasional photographs of gross pathologic specimens. A histologic diagnosis has been made in each case. The accompanying text detracts from the x-ray pictures; the pictures speak for themselves, and the editors were better silent. It is unfortunate that a brief history and clinical appraisal do not accompany each case with a differential diagnosis and final diagnosis following on the next page. With all of the cases mixed indiscriminately together, the book would then be more of a challenge for the reader.

Die gesunde und die kranke Wirbelsäule in Röntgenbild und Klinik. By Dr. Georg Schmorl and Dr. Herbert Junghanns. Ed. 3. Stuttgart, Germany, 1953, Georg Thieme Verlag, Agent for U. S. A.: Grune & Stratton, Inc., New York, N. Y.

It is surprising to see a third edition following so rapidly on the heels of the second. However, for those who have not already obtained a copy, this newer edition is to be preferred. This book is probably the outstanding work on the pathology of the spine and its correlation with the accompanying x-ray changes. It should find wide use among roentgenologists and orthopedists as a reference work. The information obtained from the systematic examination of over 10,000 spines removed at autopsy is invaluable from the point of view of determining the frequency of normal variations and the incidence of various pathologic processes.

The Temporomandibular Joint. Edited by Bernard G. Sarnat, M.D., M.S., D.D.S., F.A.C.S. Springfield, Ill., 1951, Charles C Thomas, Publisher. $4.75.

Maxillofacial surgeons and orthodontists will find this book invaluable. Within its pages, is the present sum and total knowledge of the temporomandibular joint and its relation to the growth and development of the face. It is an excellently printed book written by a group of specialists.

Roentgen Examinations in Acute Abdominal Diseases. By J. Frimann-Dahl, M.D., Ph.D., chief of Roentgen Department, Ulleval Hospital, Oslo, Norway. Pp. 323, with 305 illustrations. Springfield, Ill., 1951, Charles C Thomas, Publisher. $12.50.

This splendid book, prepared by an eminent European radiologist, deserves a wide audience. It should appeal both to the radiologist who must read films of acute abdominal diseases and to surgeons and internists who have the responsibility of handling these patients, often without benefit of immediate radiologic consultation.

In the introductory chapter the author stresses that cooperative endeavor is necessary to gain the maximum benefit from x-ray study of these illnesses. Full information about the patient's history and physical findings, careful fluoroscopy, and roentgen technique varied according to different lesions are stressed as important features in the author's methods, through which his death rate has fallen from 50 per cent to 10 per cent. This result, due largely to improvement in diagnosis, has not been achieved by routine examination and indifferent quality films.

A chapter on normal findings is followed by one on general pathologic findings, in which are considered absorption and production of intestinal gas, fluid in intestine, pneumoperitoneum, free fluid in peritoneal cavity, and lesions in chest. Then the special findings in a wide variety of diseases, twenty-eight in all, are described and portrayed in accompanying sketches and x-ray reproductions, which the American reader will be glad to know are reproduced as negative prints. Most of the x-ray pictures are well done, an important consideration in soft tissue radiography which the author is accentuating. Contrast studies, made when necessary, are also given full place. Surgeons will be interested to note that many of the diagnostic advances were the result of basic surgical experiment.

In summary, this is a very worth-while monograph, thoughtful, well constructed, and concerning an important and somewhat neglected field.

Rötgenuroscopie. By G. W. Günther. Pp. 45, with 86 illustrations. Paper covers. Stuttgart, 1953, Georg Thieme Verlag, Agent for U. S. A.: Grune & Stratton, Inc., New York, N. Y.

Called pyeloscopy by Harris in Australia and by Herbst in this country, the fluoroscopic observation of the renal pelvis and ureter filled with contrast agent gives a better idea of the dynamics of the upper urinary tract than do the conventional methods of urography with films. This is particularly true of the differentiation of stricture from spasm, and of detecting aberrations of peristalsis. However, the same information can be secured by the judicious use of serial exposures in connection with excretory urography, and by delayed exposures after retrograde pyelography.

The trouble with uroscopy is that it ties up the patient, the observer, and the equipment for long periods in order to secure information otherwise available just as accurately and much more expeditiously, and without the danger of overexposure of patient and operator inherent in fluoroscopy.

Uroscopy seems to the reviewer to be a technique for the study of the function of the urinary collecting apparatus rather than a method for widespread clinical application. The book should be read with this in mind. The illustrations are excellent, and the bibliography, with one exception, is strictly German.

ANNOUNCEMENTS

Sixth International Cancer Congress

Physicians and scientists are invited to present papers at the Sixth International Cancer Congress to be held in São Paulo, Brazil, July 23 to 29, 1954, under the sponsorship of the International Union Against Cancer. The program will include sections on fundamental cancer research, on clinical studies on cancer, and on cancer control. Registration blanks are available from the Chairman, National Committee on the International Union Against Cancer, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.

It is expected that round trip transportation by air from Miami to São Paulo will be available for about $480. Detailed information regarding travel arrangements and hotel reservations may be obtained from Dr. Brewster S. Miller, American Cancer Society, Inc., 47 Beaver Street, New York 4, N. Y.

In accordance with similar arrangements being made in other countries to coordinate participation in the Congress, residents of the United States who desire to present papers must send *five* copies of an abstract of each paper proposed for presentation to the Chairman, National Committee on the International Union Against Cancer, at the Washington address by Jan. 15, 1954. Abstracts are not to exceed 250 words and must be accompanied by a title and the name, address, academic or professional title, and institutional affiliation of the investigator or physician. These requirements do not apply to people who have been invited to participate by the President of the Congress unless application is made for travel allotments as described later.

Travel allotments of approximately $600 each will be available to a limited number of individuals requiring such assistance. Applications for travel allotments must be submitted in quintuplicate to the Chairman, National Committee on the International Union Against Cancer, at the Washington address by Jan. 15, 1954. They should be in letter form giving information concerning age, training, publications in cancer or related fields, and academic or professional status. Applicants not planning to present papers should include five copies of abstracts, as described previously, of major current investigative work. A letter from the laboratory director, or appropriate administrative officer, approving the application is also necessary.

Buffalo Surgical Society

On Feb. 18, 1954, the Buffalo Surgical Society will sponsor the Roswell Park Lecture, this year to be given by Dr. Isador S. Ravdin, John Rhea Barton professor of surgery, University of Pennsylvania Medical School, and Surgeon in Chief at the Hospital of the University of Pennsylvania.

Dr. Ravdin at that time will be awarded the Society's Gold Medal, being given for the seventh time, in honor of Dr. Roswell Park, professor of surgery, University of Buffalo, 1883 to 1914. Previous lecturers and recipients of the Medal are as follows: Dr. Allen C. Whipple (1948), Dr. Evarts A. Graham (1949), Dr. Dallas B. Phemister (1950), Dr. Frederick A. Coller (1951), Dr. Edward D. Churchill (1952), and Dr. Warren H. Cole (1953).

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